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FELIX MARTI-IBAÑEZ, M.D., Editor-in-Chief
Professor and Director of the Department of the History of Medicine,
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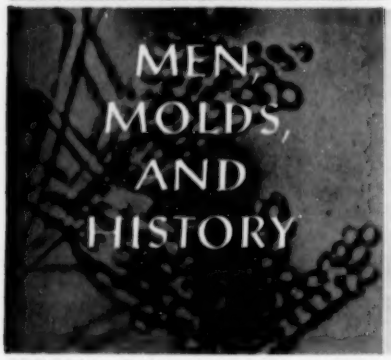

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The Scientific Basis for Neuromuscular Re-education

Harvey E. Billig, Jr., M.D., F.I.C.S., and Antoinette Perillo, M.D., F.I.C.A.

THE BILLIG CLINIC
LOS ANGELES, CALIF.

Motion is the fundamental characteristic of all living matter used for maintenance or alteration of relative position. For example, the amoeba sends out pseudopodia in flowing motion, other cells use flagellums, others, like the squid, use water jet propulsion, others, like the fish, use fins and sculling tail propulsion, others, like the snake, use gliding ground friction, others, like the bird, use aerodynamic principles. In man, motion is chiefly obtained through the coordinate use of muscle leverage.

Regardless of the type of motion, there must be an integrated network of nerve pathways to control the motion coordinately for purposeful use. The transmission of the nerve action potentials along these complicated proprioceptive, sensory, motor, and central nervous system axon pathways ends with the muscle fiber action potential of contraction, instigating motion. Incitement of the "original" action potential may be by mechanical, chemical, or electronic changes, variations of which may arise in response to reflex, psychic, memory, or sensory perception stimuli. Not all of these factors are thoroughly understood, however, considerable advance has been made since the days when "muscle training" implied an autonomous thinking capacity in the muscle itself.

Paul Weiss, Arnold Gesell, Lorente de Nó, C. S. Sherrington, and others have years ago shown the importance of maturation of axon pathways throughout the nervous system as the basis for control of muscles.

Gesell has ably led in working out the sequential development of the multiple "reciprocally interwoven patterns" of muscle function, during growth, dependent on the sequential anatomical development of the axon pathways to the stage of electrical potential carrying ability.

Pavlov called attention to the phenomena of "conditioning," and this laid the groundwork for our understanding of the multiple number of "conditioned" axon

pathways controlling habit patterns of muscle function. These are superimposed on the fundamental, developmental, maturation patterns referred to by Gesell. These conditioned habit patterns become as fixed as the maturation patterns, and it is said that once acquired, they are never lost. They may, however, be inhibited by superimposition of other conditioned patterns. This explains the frequency with which an individual will tend to revert to a previous pattern, e.g., the "hitch" of a baseball pitcher or batter, or the continuance of automatic activity of the left leg after changing to a clutchless automobile.

In neuromuscular education or re-education, it is therefore necessary to ascertain the stage and sequence of developmental maturation patterning and the specific conditioned patternings of the patient. For example, it would be not only useless, but detrimental, to approach a 3-year-old child in terms of patterns of function that he has not as yet developmentally reached, or to approach any patient in terms of patterns that conflict with ones he has acquired as a fixed part of the coordinate use of his musculature.

Proper function requires full and normal development followed by maintenance of the integrity of both the axon pathways and the bony-musculature system. Errors of development, such as for example, spina bifida, may include deficient innervation to the periphery so that motor, sensory, or proprioceptive defects are present, and trophic disturbances may further complicate care.

There are a number of types of dystrophies to include progressive muscular atrophy, pseudohypertrophic familial dystrophy, amyotonia, postpartum dystrophy, Guillain-Barré syndrome (chronic poliomyelitis, Landry's ascending paralysis), and poorly defined neurological afflictions to include multiple sclerosis and lateral sclerosis, and poorly understood neuritides to include diphtheritic, diabetic, subacute combined sclerosis (? vitamin B_{12} deficiency), and beriberi (? vitamin B deficiency), the basic mechanisms of causes for which are so poorly understood that constructive methods of neuromuscular re-education will have to await further research.

Myasthenia gravis, representing one of the dystrophies with a defect of creatine metabolism, has been intensively studied and presents a type of neuromuscular function where each succeeding contraction grows rapidly weaker and soon a rest is necessary before further force can be obtained. Experts in neuromuscular physiology, notably Schwab of Harvard and Tether of Indiana, believe that this "myasthenia gravis type" of decline of power is a characteristic widely dispersed throughout the populace and in general going unrecognized due to its subclinical degree (i.e., not presenting the full-blown signs and symptoms of myasthenia gravis). At the Billig Clinic a number of patients presenting poor endurance have been investigated by Billig and Morehouse, and we are inclined to agree with the views of Schwab and Tether on this point. A useful test is that of curare, as described by Tether. It is of utmost importance that these observations be followed up. Examination of students in our school systems may well prove that these children who "can't try" or "can't do" in physical performance may really be fundamentally unable to demonstrate comparable power and endurance (e.g., "push-ups" are a good test). How many of our "poliomyelitis" and other patients being given neuromuscular re-education have also this type of neuromusculature?

Enhancement of power by means of progressive resistive exercises (De Lorme schedule) has long been recognized by weight lifters and demonstrates the fundamental principle of gaining increased use through use.

Reports from Germany (Muller) of the very small amount of exercise necessary to maintain neuromuscular performance have instigated re-evaluation. In view of the foregoing it would be interesting to know just what anatomico-physiological-neuromuscular types were included in this study.

"Fatigue" is a vaguely defined term frequently used without designating the particular type or locale (i.e., muscle fiber, nerve, central nervous system, biochemical, enzymatic, hormonal). As demonstrated by Morehouse, the normal site of fatigue limitation is neural rather than muscular, so that this concept must be evaluated in any discussion of neuromuscular performance. This poses problems of great magnitude in evaluation of treatment for the various types of neuromuscular disabilities and again emphasizes the necessity for extensive research.

When the proprioceptive afferent nerve fibers from the muscle spindles carrying the sense of muscle position are interrupted, the individual is unable to use the muscle or contract it, even though full sensory and motor supply is otherwise unimpaired. This raises the question of how much of neuromuscular defects in various disorders may actually be impairment of proprioceptive sensation.

A tabetic may present a typical positive Romberg test with the eyes closed, or tend to fall down if he leans over, with eyes closed, to wash his face. However, if he keeps touching the wall while his eyes are closed, his muscle orientation returns, the positive Romberg becomes negative, and he keeps his balance. It is interesting to speculate about how it could be possible that just touching the wall with the hand or using his sense of vision could restore the "muscle sense" to his legs, and by what neuron pathways.

History is replete with examples of rhythm-training enhancement of performance of work requiring coordinate muscular effort, e.g., the "Volga Boat Song," the rope skipping, punching bag, and road work of the boxer, the repetitive steady pacing by exercise boys with "good sense of timing" in horse training.

Again utilizing the principle of enhancement of use through use, we have attacked the problem of the clumsy individual, with poor coordination, by means of proprioceptive training through intense, active rhythm exercises carried out to a set pace. These exercises are done to a steady pace "in the swing" of the rhythm daily for as long a period of time as possible, certainly for an hour or more in half-hour periods. Rope skipping with a heavy rope so that it will keep a steady pace is satisfactory. In infants the arms and/or legs may be guided in rhythmic motion to a phonographic waltz tune. The infant usually loves the rhythm and cooperates well, and the repetitive motion needs only guidance. We have observed that in the Negro race, where rhythm is a part of the daily life from infancy on, there seldom is a discoordinate child (Watts Crippled Children's Clinic at Los Angeles City Health Department). The natural impulse of the baby is to rock forward and backward on his arms, chest, and haunches, then later to pull himself up by the bars of the crib and shake backward and forward to rhythm. This is disturbing at night, but should be regarded as important to the infant's development, and hence encouraged.

The use of zipper sheets is to be condemned, since they inhibit this natural impulse, and it is unfortunate that the old trundle bed, rocking in its rhythm and encouraging the infant to synchronize his muscles accordingly, has gone out of style.

Using the active rhythm exercise training, the child rapidly develops his proprioceptive sense of coordination, to catch up with and even pass his proper developmental age Gesell pattern. Several babies, experimentally started on the intensive rhythm exercises at the age of 2 weeks, reached the stage of spontaneous walking at the age of 7 months. At the age of 5 years children will reach the norm within four months. At the age of 8 years it takes six to eight months. After the age of 14 years in girls, and 15 years in boys, the improvement is slower.

An easy method of scoring progress is to have the child stand with back to a wall on which is marked a grid. The child then raises the arms to the horizontal level, closes the eyes, tilts from side to side several times, and then, with eyes still closed, attempts to stand as straight as possible with arms outstretched as close as possible to horizontal; a record film is then taken.

Relaxation of one set of muscles, in order to allow the opposing muscles to operate, is under delicate balance, so that deviation of axon pathway control from higher centers* may result in disabilities such as parkinsonian tremor and "stiffness" of muscles. Rebalance of muscle power may be regained by means of central axon pathway re-education through repetitive conditioning, using very slow passive motion carried out continuously for an hour or more daily. This is tedious for the therapist. The very slow passive motion forces the central nervous system axon pathways continually to recognize the regular changing position of the muscles (picked up by the spindle cells) and encourages the resumption of normalcy of axon pathways by this repetitive conditioning. In fact, the more the treatment is carried out, the better the response, as is true of all repetitive conditioning. This method is of value in spastic conditions, either congenital or acquired (e.g., spastic hemiplegia).

Muscle "spasm" involving the lower motor reflex arising from joint pain or infection, muscle contusion or tear, e.g., "Charley horse," or as found in spastic torticollis is best treated by rest and elimination of the local etiological cause.

Muscle cramps (usually termed "night cries" if they occur at night) aggravated by exercise ("stitch in the side") due to a low calcium level (frequent) may be "pulled out" by gentle, steady stretch on the cramped muscle and, of course, provision of adequate calcium intake.

Deficient muscle power often results from a loss of a part of the lower motor neuron axons, either from avulsion (e.g., Erb's), peripheral nerve injuries, or poliomyelitis. In these types there is then left a considerable number of denervated muscle fibers that revert to a semiembryonic state (motor unit is 120 or so muscle fibers/motor axon). Five to seven days after denervation, the muscle fibers begin to give rise to a fibrillation potential measurable by the needle electrode electromyographically. The atrophy of these denervated muscle fibers may in time give

* It should be mentioned here that surgical section or sclerosing solution interruption of the proper axon pathways in the brain will result in immediate alleviation of the parkinsonian tremor.

way to degeneration and absorption. In the meantime, if the remaining live motor axons are given the opportunity, they will increase their branching (arborization) to reinnervate also some of the denervated muscle fibers, resulting in an enlargement of the motor unit with concomitant increase (restoration) of power output of the muscle. Again, the principle of increased use through use may be utilized by placing a demand of use on the muscle during the increasing arborization (reinnervation) period.

In rabbits, slightly lower on the phylogenetic scale, the remaining live motor axons will spontaneously increase their arborization to resupply the denervated muscle fibers (Van Harreveld). In the *Ambystoma*, still lower on the phylogenetic scale, a complete new extremity can be regrown.

It is possible that the natural muscle power recovery period of the paretic poliomyelitic patient is explained, at least in part, by this mechanism of spontaneous arborization enlargement of the remaining intact motor units.

A similar mechanism is well recognized in sensory nerve regrowth. When the sensory nerve supplying an area of skin is irrevocably removed, then, and not until then, will the sensory nerves supplying adjacent skin areas increase their branching to resupply the denervated area.

Neuromuscular re-education can be facilitated by adding the use of the senses of vision and hearing to that of proprioceptive feel. The electromyograph connected to a loudspeaker has also made this possible. Surface electrodes over the muscles are satisfactory and the patient is told to watch the screen of the cathode ray oscilloscope and listen to the sound. Then, with each contraction of the muscle, the patient is urged to increase the wave forms appearing on the scope, simultaneously increasing the sound of them coming over the loudspeaker. An ingenious innovation is to place the surface electrodes over the opposing muscles that are supposed to relax (as in spastics) and tell the patient to practice muscle use making less wave forms appear on the scope, and simultaneously, less noise.

Remarkable discriminatory ability of control of motor units of muscles may be demonstrated this way.

Years ago, from the research laboratories of the California Institute of Technology, prior to the advent of routine clinical electromyography, Wiersma made a detailed study of single motor units that had been found (Wiersma, Van Harreveld, and Billig) as the sole residual functioning units in specific paretic postpoliomyelitic muscles. It was found that these patients could easily learn (many had learned spontaneously) to turn these single motor units on and off at will.

Subsequently, in the department of physical medicine of the College of Medical Evangelists, a physical therapist and a professor (Dr. Clarence Dale), using both surface and needle electrodes, demonstrated on themselves this ability for discrimination between individual motor units. They became so expert that they could select a motor unit in one of their muscles and turn it off and on selectively without stimulation of any of the surrounding motor units.

By repeated trials it is easily possible to learn to turn two or three or more adjacent motor units on and off, selectively, thus demonstrating specifically the possibilities for use of the electromyograph in neuromuscular re-education.

Axon pathways in the central nervous system controlling patterns of muscle function develop systematically during growth according to a set maturation sequence. On these patterns are superimposed countless acquired (conditioned-habit) patterns. The individual may be recognized by his gait, in the same way that the children in the pediatrics ward can selectively recognize their approaching, yet unseen, nurse or physician by the sound of the gait-patterned steps in the hall. A child (or adult for that matter), when walking in its sleep, will demonstrate the same axon pathway-controlled gait pattern as that demonstrated in the conscious state.

In view of the foregoing discussions concerning the demonstration of patterns of axon pathways as the basic guide for neuromuscular activity and in view of the extreme simplicity with which new habit patterns may be acquired by conditioning, an investigation into the possibilities, in neuromuscular re-education, of adjustment of axon pathways by means of suggestion therapy under hypnosis has been made at the Billig Clinic.

Good results in neuromuscular re-education depend very much on the patient and physician being in perfect rapport. When the patient accepts the method of procedure, he is assured that his cooperation, in following suggestions made, will bring about the desired results. The first step is to make him aware of how much the mind affects body reaction. He is taught how to get tension in the muscle consciously, and then how to relax these muscles. For an example, let him feel the difference in the muscles when he clenches his fist tightly, and when he opens his fist. This alternation of tension and relaxation impresses him.

The next step is to teach him muscle control through the mind. Using a pendulum, he is taught to think the direction he wishes it to swing, without moving his forearm or fingers.

The patient is fully aware now that he can, by merely thinking, direct body reaction. All this is done to establish a closer rapport between the physician and the patient and to clear the patient's mind for specific attention. The important part of the entire procedure is to teach him how to relax the skeletal musculature in his body. This is done by having the patient in a comfortable position, breathing deeply and listening attentively. The physician, repeatedly, in a soft, soothing, and rhythmical voice, gives the suggestion of complete relaxation. With each succeeding practice session, complete relaxation can be achieved, quicker and deeper than at the previous session. When the patient is in this state of complete relaxation ("light hypnosis"), the desired suggestions are given, over and over again, until the patient develops his own method of autosuggestion, which gradually fixes as a repetitive habit pattern (conditioning).[7,8]

Initially, the patients selected were those with rather simple, uncomplicated problems, e.g., tendon transplants. In these patients, the axon pathways must rearrange to accommodate for the incorporation of coordinate performance of the muscle in its new (different) function. For example, the posterior tibial and peroneal muscle tendons were redirected to the dorsum of the foot so as to enhance dorsiflexion of a drop foot. For more than six months postoperatively, the patient, a 26-year-old woman, was unable to develop the "feel" of use of the transplanted muscles, in

spite of intensive routine neuromuscular re-education, with the additional aid of the electromyograph. The tendency was to hold the foot rigid (splinted) and walk on it as though on a peg. This patient responded well to hypnosis at the first treatment, but was not carried deep enough to be "completely under." Then, suggestion for the new use of the muscles of the foot were repetitively given. On return to the usual conscious state, the patient was found to be using the transplanted muscles properly and was so pleased that she had to walk around the clinic in high heels, demonstrating what a wonderful thing the physician had done for her, and she could hardly wait to get home to surprise her mother. The patient was treated several times subsequently, at weekly intervals, in order to "reinforce," although this may not have been necessary. Other patients have varied in their response to the "hypnosis" so that at times it has taken several visits, at weekly intervals, before they relax sufficiently to be carried "part way under." In no instance has the patient been carried to the point of "complete" hypnosis, a degree of conscious volition being still present. Various types of other neuromuscular disabilities are now being treated. It is considered that the rearrangement of axon pathways by "hypnotic suggestion," so as to enhance proper neuromuscular coordinate function, is a rapid form of conditioned reflex training.

The possibilities for using this method in order to eliminate harmful axon pattern habits of use of muscles is now being investigated.

SUMMARY

The importance, to coordinate useful muscle function, of the concept of neuronic transmission of action potentials by patterns of axon pathways is outlined.

The significance of developmental maturation axon pathway patterns (Gesell) and conditioned axon pathway patterns is illustrated.

Attention is called to the possible prevalence in the populace of the "myasthenia gravis type" of decline of power in successive muscle function.

The significance of progressive resistive exercises, fatigue, and the as yet unknown role that defects of proprioceptive (muscle spindle cells) sensation play in the muscle performance is pointed out.

Improvement of coordination of axon pathway patterns by means of exercises to rhythm is noted.

A means of aiding restoration of control of balance of power in spastics is proposed.

Reflex muscle "spasm," muscle cramps, and the importance of calcium are mentioned.

The normal distribution of the action potential by means of arborization of the motor axon to 120 or so muscle fibers is reviewed, and an example is given of a way to obtain increased power in paretic muscles by increasing the arborization of the residual motor axons.

The significance of single motor unit control and the use in re-education of the senses of sight and hearing by means of the electromyographic machine hooked to a loudspeaker are analyzed.

A means of rapid, repetitive habit conditioning of axon pathways controlling muscle function by means of hypnotic suggestion is described.

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The Use of Hydroxyzine in Internal Medicine

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Two of the problems most frequently encountered by the internist are the treatment of psychophysiological ("psychosomatic") disorders and of emotional factors associated with functional disturbances. It has been estimated that in approximately two thirds of the patients seen by the internist, the mechanism through which psychic tension or anxiety finds bodily expression must be taken into account and alleviated when possible. Approximately one half of this group of patients are those in whom no specific organic disease can be found to account for the illness. The remainder of the group may have symptoms not explained by the illness or out of proportion to the existing condition.

Psychophysiological autonomic and visceral disorders are reactions in which emotional factors often play a causative role. The psychophysiological disorder may be manifested as a skin reaction (e.g., neurodermatitis), respiratory disorder (bronchial spasm, hyperventilation), cardiovascular reaction (neurasthenia, paroxysmal tachycardia, labile hypertension), gastrointestinal disorder (peptic ulcer, chronic gastritis, ulcerative colitis, pylorospasm, "irritable colon"), genitourinary disturbance or menstrual disorder, endocrine reaction, reaction of the nervous system (general fatigue), and many other possible variations.

Establishing a good physician-patient relationship is an important factor in treating such reactions. The recent introduction of psychotherapeutic agents has given the physician a new aid in the treatment of psychophysiological reactions. However, because of the emotional factors to be considered in these disorders, the type of physiological reactions involved, and the fact that the majority of the persons seen by the internist are ambulatory patients with daily responsibilities at home or at work, certain requirements must be met by any oral psychotherapeutic agent selected. Ideally, the drug employed should have a wide range of effectiveness and provide a calming effect without cortical depression, which would produce drowsiness. In addition, the agent should not add to or aggravate the existing problem by producing complications such as increased gastric acidity, serious hypotensive reactions, addiction, or toxic effects on parenchymatous organs.

Hydroxyzine pamoate* was selected for this study since it appears to be an agent well suited for treatment of psychophysiological disorders seen in office practice. Hydroxyzine is reported to have a broad range of application, providing antihistaminic action and direct and secondary skeletal muscle relaxation with a high degree of safety.[1–10] Hydroxyzine pamoate does not appear to produce depression, will not increase gastric acidity, which is particularly important in treatment of the ulcer patient, produces no serious hypotensive reaction, and is not addicting. Blood

* The trade name of Chas. Pfizer & Co., Inc., for hydroxyzine is Vistaril.

TABLE I

Results of Treatment with Hydroxyzine Pamoate

Diagnosis	Patients			Results				Side Effects
	Male	Female	Total	Excellent	Good	Fair	Poor	
Anxiety state	6	11	17	5	9		3	Drowsiness, 3 Numbness of arms, 2
Hypertension	5	5	10	5	4	1		
Duodenal ulcer	2	4	6	4	1	1		
Arthritis and arthralgia	1	3	4	1		2	1	
Pylorospasm	2	2	4	1	1	2		
Bronchitis	1	2	3	2	1			
Ulcerative colitis	1	2	3	1	1	1		
Depressive state	1	1	2		1	1		
Diabetes		2	2	1		1		Drowsiness, 1
Hyperthyroidism		2	2		2			Lightheadedness, 1
Paroxysmal tachycardia		2	2		2			Drowsiness, 1
Manic-depressive state		1	1				1	Overstimulation, 1
Neurodermatitis		1	1			1		Paresthesia, 1
Miscellaneous psychophysiological conditions*	2	1	3	1	2			
Miscellaneous other conditions†	2	5	7	4	2	1		
	23	44	67	25	26	11	5	

* Included under miscellaneous psychophysiological conditions: Hypochondriasis, cardiac neurosis, chronic headache.

† Included under miscellaneous other conditions: Hypothyroidism, mitral stenosis, herniated intervertebral disc, asthma, epistaxis, gastric polyposis, severe obesity.

or liver toxicity effects or parkinsonism has not been reported despite prolonged administration of hydroxyzine.[1] One additional and unique advantage of this drug is its effectiveness in treatment of cardiac arrhythmias, and its ability to allay the associated anxiety and apprehension.[11]

METHOD

Sixty-seven patients (20 men, 47 women), ranging in age from 19 to 75 years, were treated for anxiety, tension, nervousness, or depression associated with various psychophysiological or functional disturbances (see Table I). For 66 of the 67 patients, the dosage of hydroxyzine pamoate was 1 capsule (50 mg.), taken two to four times daily. One prepsychotic patient received 50 mg. of hydroxyzine hydrochloride intramuscularly, twice daily. Duration of therapy ranged from 2 to 30 days.

RESULTS

Hydroxyzine pamoate was found to be effective in 62 of the 67 patients treated (see Table I). Response to therapy was excellent in 25 patients, good in 26, fair in

11, and poor in 5 patients. Patients in whom the response was classified as excellent, good, or fair showed remission of anxiety, tension, nervousness, and insomnia, as well as a lessening of symptoms associated with various functional and psychophysiological disturbances.

All of the 9 patients suffering from peptic ulcer, ulcerative colitis, or gastric polyposis exhibited fair, good, or excellent responses with alleviation of gastrointestinal and emotional symptoms. In none of the 9 patients reported was there clinical evidence of any increase in the gastrointestinal disturbance. Six of the 11 hypertensive patients showed a decrease in blood pressure with administration of hydroxyzine pamoate alone. An antiarrhythmic effect also was observed in the 2 patients with paroxysmal tachycardia.

SIDE EFFECTS

Ten of the 67 patients reported various mild side effects including drowsiness, numbness, overstimulation, lightheadedness, or paresthesia. In 7 of the 10 patients, drowsiness or overstimulation disappeared within one or two days, though therapy was continued; paresthesia was eliminated by a reduction in the daily dosage. Since side effects persisted longer than two days in the 3 remaining patients, therapy was discontinued; however, in no instance was any serious reaction observed.

SUMMARY AND CONCLUSIONS

This study confirms the previous observations that hydroxyzine pamoate is ideally suited for use in the practice of internal medicine. Hydroxyzine pamoate was found to be a very effective agent in treatment of psychophysiological disorders and alleviation of emotional symptoms associated with various functional disturbances.

Hydroxyzine pamoate appears to have a broad range of application and safety. Its calming effect is free of such side effects as depression, increased gastric acidity, serious hypotensive reactions, or blood and liver toxicity effects that may be associated with other drugs similar in use.

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Combined Steroid-Ataractic Therapy in Allergy

William C. Grater, M.D.

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The successful management of allergic disorders is often a challenge to the physician. The symptomatology is influenced by a number of factors other than hypersensitivity, including infection, weather, and hormonal imbalance as well as psychogenic influences. Eisenberg[1] found ataractic drugs to be of therapeutic value for allaying tension and anxiety in approximately one third of a series of allergic patients.

This study deals with an evaluation of the combination of two well-established drugs,* prednisone and perphenazine, in the treatment of allergic disorders. Prednisone, widely used in allergy,[2] is a potent anti-inflammatory and antiallergic agent.[3] Perphenazine is one of the most potent of the phenothiazine ataraxics.[4] In addition, it also has some antiemetic and antipruritic action.[5] The combination of these agents seemed indicated in the total management of the allergic patient.

PROCEDURE

Ambulatory patients suffering from allergies of the conjunctiva, nose, lungs, and skin were chosen. An attempt was made to eliminate those with obvious infection or to control this with antibiotics.

The dosage varied from 2 to 8 tablets daily for one or several weeks. Most patients received 3 to 4 tablets daily.

Comparative evaluation of cases of skin allergies and allergic conjunctivitis was made with progress color photography. Involvement of the nose was evaluated by inspection of nasal blockage, rhinorrhea, and nasal mucosa before and after therapy. Pulmonary function was determined by the ½-second timed vital capacity and total vital capacity measurements using a Collins Vitalometer, whenever possible.

RESULTS

The results are shown in table I. Of 161 patients, 143 responded well. To confirm results, 62 of these patients were treated with a combination of 2.5 mg. prednisolone and 2 mg. perphenazine. The results are shown in table II. It was noted that there was little difference between prednisone and prednisolone in equal doses when combined with the same amount of perphenazine. There was no evidence that prednisolone acted more swiftly than prednisone.

The side effects were of a minor nature in this short-term study (table III). From a practical viewpoint, the most significant side effect of short-term steroid therapy is nervousness. Although this is seldom mentioned in steroid studies, it is one of the

* The trade name of Schering Corp. for the combination of prednisone and perphenazine is Sterotril. Each tablet contains 2.5 mg. prednisone and 2 mg. perphenazine. The drug was supplied for this study by G. Kenneth Hawkins, M.D., Division of Clinical Research, Schering Corp.

TABLE I

Results of Therapy with Prednisone and Perphenazine

Disorder	Total patients	Satisfactory	Unsatisfactory
Allergic rhinitis	62	54	8
Allergic rhinitis and asthma	77	67	10
Urticaria	7	7	0
Atopic eczema	7	7	0
Contact dermatitis	8	8	0
Total	161	143	18

TABLE II

Results of Therapy with Prednisolone and Perphenazine Compared with Prednisone and Perphenazine

Disorder	Satisfactory	Unsatisfactory	Same as prednisone	Prednisolone better	Prednisone better
Allergic rhinitis	26	1	20	3	4
Allergic rhinitis and asthma	25	1	19	4	3
Urticaria	3	2	3	1	1
Atopic eczema	2	—	2	0	0
Contact dermatitis	2	—	2	0	0
Total	58	4	46	8	8

TABLE III

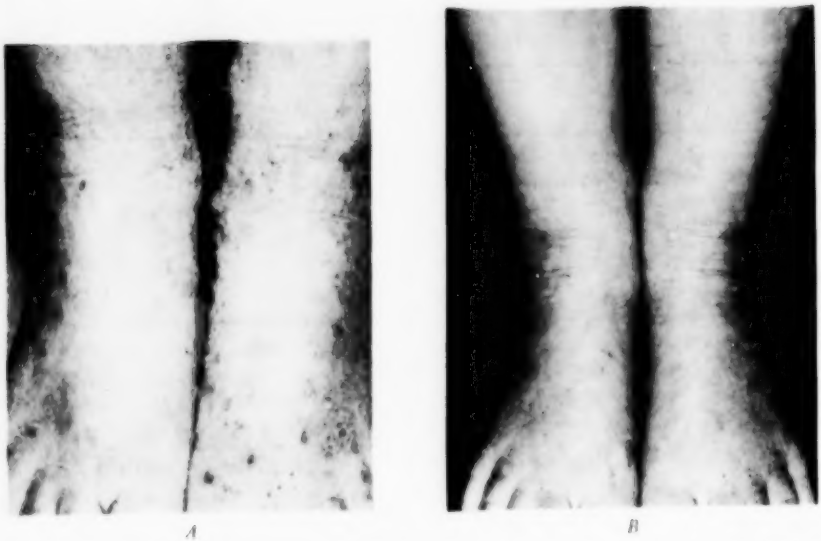
Side Effects in 161 Patients

Side Effect	Number of patients
Gastrointestinal distress	1
Drowsiness	9
Dizziness	3
Depression	4
Nervousness increased	4

TABLE IV

Special Effects of Steroid in Combination with Perphenazine

	Number of patients
Less nervous than on prednisone alone	22
Less prednisone required than with prednisone alone	19
Same prednisone requirement as with prednisone alone	18
Prednisone dosage inadequate	4



A *B*

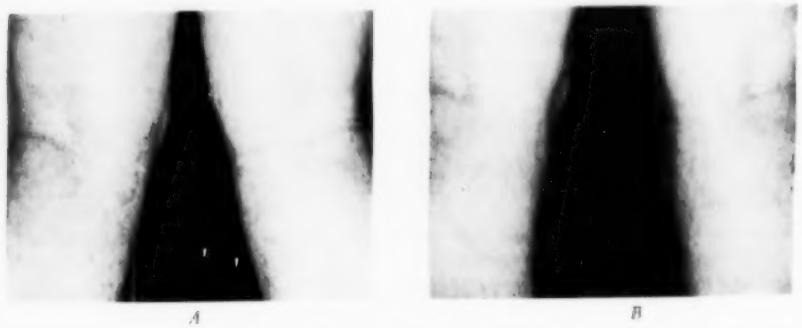
FIG. 1.—A patient with chronic disseminated atopic dermatitis before (*A*) and after (*B*) five days of therapy. The combined steroid-ataractic therapy had a greater antipruritic effect and provoked less nervousness than did steroid therapy alone.

major reasons that patients discontinue therapy. The perphenazine decreased nervousness in 76 of 80 patients who complained of this symptom.

The response to steroid is summarized in table IV. Perphenazine-prednisone was superior to prednisone alone in 22 patients. An actual reduction of prednisone dosage was achieved in 19 patients who had been treated with prednisone alone.

DISCUSSION

Early in the study it became apparent that the prednisone- or prednisolone-per-



A *B*

FIG. 2.—Same patient as in figure 1.

A *B*

FIG. 3. Same patient as in figure 1.

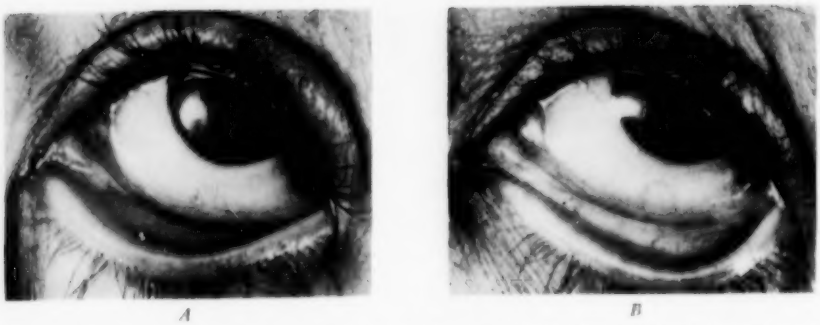
phenazine combination was particularly suited to certain types of patients such as those with atopic or contact dermatitis. Psychological factors are often involved. Itching is a prominent complaint. In fact, the itch-scratch cycle must be broken before any satisfactory results can be achieved.

Anxiety is often marked in asthma. The patient is gasping for air, stimulated by adrenergic drugs, and difficult to manage. Nevertheless, successful therapy demands that the patient follow the prescribed regimen. The calming effect of the ataraxic enhances his confidence and cooperation.

One of the greatest disadvantages of steroid therapy in allergies is the difficulty at withdrawal. Having breathed comfortably for the first time in years, the patient is

A *B*

FIG. 4. A patient with seasonal allergic conjunctivitis (hay fever) before (*A*) and after (*B*) seven days of therapy.



A *B*

FIG. 5. A patient with seasonal allergic conjunctivitis (hay fever) before (*A*) and after (*B*) seven days of therapy.

reluctant to return to his former state. As many pulmonary physiologists have noted, decrease of pulmonary function is not entirely responsible for symptoms. The patient's awareness of his respiratory effort also is causative. Addition of an ataraxic decreases this anxiety. It was noted that occasionally in asthma a lower steroid dosage can be used with an ataraxic than is possible on steroids alone. However, the patient's judgment of results is not necessarily confirmed by pulmonary function tests. It is relatively easy to withdraw this type of patient from combined therapy by using the ataraxic alone.

Poorest results were noted in intrinsic asthma where the steroid dosage was often

A *B*

FIG. 6. A patient with contact dermatitis due to chromium before (*A*) and after (*B*) eight days of therapy. The antipruritic effect was marked.

inadequate for suppression. The dosage of the combined steroid-ataractic tablets required to control symptoms provoked excessive drowsiness.

SUMMARY

Combined steroid-ataractic therapy is of considerable benefit in treating allergic patients with emotional problems. The calming effect permits greater patient cooperation and better long-term results. The best results were noted in asthma associated with anxiety and in allergies of the skin.

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Fractures in Children: Conservative Management of Shaft Fractures*

W. Compere Basom, M.D., M.S.Or.

EL PASO, TEXAS

The treatment of fractures in growing children is somewhat different from that in adults. In adults, usually a very accurate reduction is indicated both from the standpoint of encouragement of union and for a good functional result.

In children, the added factor of bone growth aids in the management of the fracture. Therefore, the surgeon can be primarily concerned with alignment and leave the apposition more or less to nature. In other words, the growth of the bone will fill in through the "offset." The prominences will disappear, and if there is time left in the growth period of the child, the bone will resume a more or less normal or completely normal anatomical appearance, even by roentgenographic examination, with the passage of time. Trauma stimulates epiphyseal growth so that shortening may also be compensated for by growth.

The surgeon should try to avoid surgery in the management of most shaft fractures of the long bones. Surgery is rarely indicated in children. The surgeon must determine how much bone growth the child will have and must determine whether or not his reduction is satisfactory for a good functional result. However, it is probable that excellent results can be obtained in many instances in which the roentgenograms do not look favorable at all. In other words, the patient, rather than the roentgenograms, should be treated and a strong attempt should be made to avoid surgery if at all possible.

However, in certain cases there are definite indications for surgery in children. One should not expect growth to eliminate deformity near joints, and fractures in or near joints should be accurately reduced even if surgery is required. In the midshaft of the bones, however, a much more conservative policy can be utilized. Fractures in this region need merely to be aligned properly. The apposition of the fragments can be left in quite a bit of offset. In some instances even almost complete offset or loss of apposition can still give a very good result and in a year or so even an almost normal roentgenographic appearance. At times a normal roentgenogram will result.

It is up to the treating physician to balance the patient's age, his further period of expected growth, and his size with the problem of whether or not the patient needs conservative or radical treatment. Fractures in the mid-portion of the femoral shaft, in the shafts of the forearm bones, in the humerus, and also in the clavicle, particularly, can be treated conservatively in a majority of instances, even an almost complete offset of the fracture can resolve itself by growth into a very good apposition appearance later on, even by roentgenogram, in these areas. In the forearm bones it has been the author's experience that, provided the length and alignment

* Presented at the 19th Annual Meeting, The American Fracture Association, October 2, 1958, Oklahoma City, Oklahoma.

FIG. 1. Fracture of mid-third of the shaft of the clavicle with complete overriding, or offset, of fragments, in a 14-year-old boy.

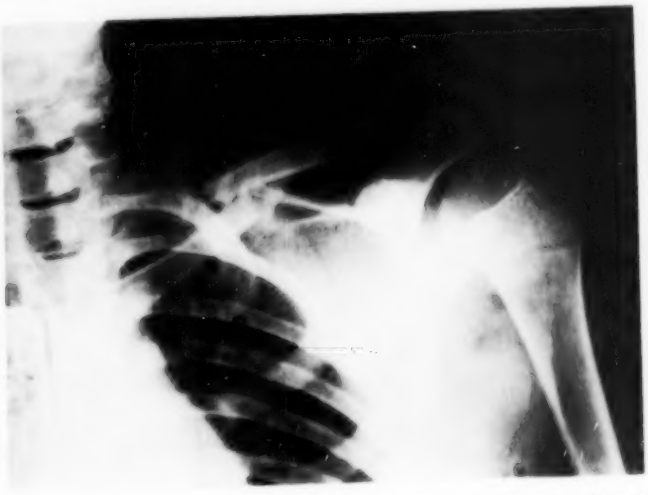

FIG. 2. Same patient, Sept. 21, 1954; callus is bridging the fracture site. There is still complete loss of apposition.

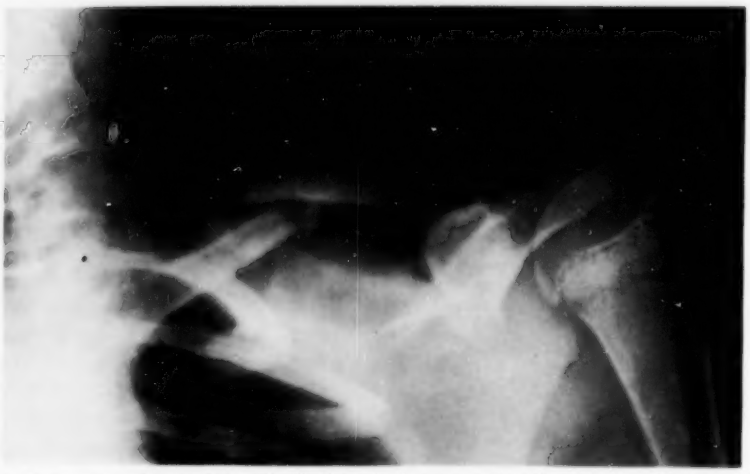

FIG. 3. Same patient, Oct. 12, 1954, callus bridging the fracture. Clinically the fracture is solidly united.

are maintained, even a complete offset of one bone can be compensated for by a further period of growth.

Rotation of the bones, particularly the radius and ulna, is very important. The position of the forearm should be carefully considered, that is, whether the forearm should be put up in pronation, mid-position, or supination.

FIG. 4. Same patient, April 5, 1958. The patient returned because he had injured the shoulder. This roentgenogram shows that the old fracture site has been completely obliterated by bone growth and the patient has an excellent result, both clinically and roentgenographically.

Usually, the more comminuted the fracture, the more conservative the treatment. In fact, there are some cases in which surgery and open reduction attempts are definitely not indicated. Extreme comminution does not lend itself to open reduction and firm internal fixation. Hematoma and callus are jeopardized at times with open reduction procedures. In many cases conservative treatment with skeletal traction in the femur or casts and double fixed traction or more conservative treatment of that type is still indicated.

Soft-tissue interposition may rarely occur at any fracture site at any age. This can be suspected if the bony clicking and rubbing together and crepitus feeling are not present. For instance, if a child with a fractured femur suspended in overhead adhesive traction does not have a definite clicking sensation of the bones on palpation or if the patient does not become comfortable in a few days, soft-tissue interposition should be suspected. A light anesthetic can be given so that a little more intensive palpation can be carried out. If there is a rubbery sensation at the fracture site and the bones cannot be felt to grate together, then an open reduction is indicated. In the author's experience this has been rare.

Figures 1 to 4 illustrate a case of fracture of the clavicle with complete offset treated conservatively, with only good alignment being obtained. There was complete loss of apposition. A roentgenogram taken 3½ years later (fig. 4) revealed a normal clavicle and the apposition had been completely returned to normal by bone growth.

In conclusion, it should be stated that the majority of fractures in children can be treated conservatively; however, in certain cases surgery is definitely indicated. In particular, fractures near or in the joints and those with circulatory embarrassment should be seriously considered for surgery. Soft-tissue interposition may be an indication for open reduction.

Erratum

In the article on page 543 of the September, 1959, issue of the *International Record of Medicine*, "The Use of Chlorothiazide and Hydrochlorothiazide in Hepatic Edema," by Charles M. Thompson, M.D., and Vincent C. Desiderio, M.D., the second sentence of the first paragraph on page 543 should read: "These include . . . decreased sodium and water excretion . . ."

The Pediatric Management of Emotional and Behavioral Disorders*

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The management of emotional disorders in childhood has assumed a place of first importance in pediatric practice and more especially in social pediatric practice. Of patients seen personally for the first time in the children's outpatient department of a large general hospital in 1957, approximately 36 per cent were referred on account of emotional problems. The corresponding figure for 1947 was 19 per cent. This does not necessarily reflect an increase in the incidence of emotional problems, but does give an indication of the magnitude of the challenge to the pediatrician. The purpose of this paper is to outline the methods employed and the results obtained in a series of 367 children studied over a period of 12 years.

THE CLINICAL MATERIAL

During the period January, 1947–December, 1956, approximately 1800 children were seen personally at the outpatient department on account of behavioral disorders of all degrees of severity. About 70 per cent of these children were adequately dealt with at routine outpatient sessions carried out under conditions that were not ideal. Four hundred and twenty-one of the children presented special difficulties in diagnosis and management and were studied at leisure away from the distractions of a busy teaching hospital outpatient department. The 421 children included 15 with a history of epilepsy, 10 with a history of asthma, 12 with near relatives who had been or were being treated for psychoneurotic or psychopathic states, and 7 whose severe emotional disorders were accounted for entirely by wartime experiences. For the purposes of the present study these 44 children, together with 10 children living in foster homes, were not included in the series, leaving a total of 367 children.

Of these 367 children, 65 were less than 5 years old and the ages of the remaining 302 ranged from 5 to 15 years. Distribution of the children according to age and sex is summarized in table I.

Boys predominated among those less than 13 years old and girls among the few older than that.

In table II are summarized the reasons given by physicians for referring the children. Ten children were sent with a tentative diagnosis of mental deficiency. The diagnosis in these cases was based on a clinical misinterpretation of the behavioral disorders.

THE CLINICAL STUDY

First consultations in the hospital outpatient department were limited to obtaining a detailed history and carrying out a thorough physical examination. Children

* Based on lectures given at the Universities of Bergen and Oslo, Norway.

TABLE I

Age and Sex

	Age, yr.							
	2-5		5-10		10-13		13-15	
	M	F	M	F	M	F	M	F
Number of children	59	26	108	61	52	47	14	20
Per cent	63	40	64	36	52	47	41	59

with organic disorders were excluded. At subsequent consultations historical, clinical, and sociological findings were integrated and supplemented. The pediatric almoner, who is a member of the university departmental staff, took an active part in the great majority of the consultations. When the need arose in individual cases for skilled technical assessment of intellectual and emotional age, the help of medical officers with special experience in the school health service was obtained.

The total incidence of different disorders in the series is given in table III. In the case of every child included in the series the behavioral disorder that had prompted reference of the child to hospital was only one of several and often many disorders. A further frequent finding was that the disorder prompting reference was not the most significant or the most deeply entrenched disorder in the child.

Success in management was dependent on recognition of factors contributing to the emotional and behavioral disorders. Impressions concerning the relative im-

TABLE II

Reasons for Reference

	Children (367)			
	Age, yr.			
Disorder	2-5	5-15	Total	Per cent
Difficult to manage	27	64	91	25
Extreme nervousness	7	50	57	15
Speech disorder	22	21	43	11
Sleep disorder	4	11	15	4
Mentally deficient	3	7	10	3
Enuresis	1	41	42	11
Encopresis	1	17	18	4
"Paras"		26	26	7
Scholastic problem		20	20	5
Delinquency		15	15	4
Movement disorder		10	10	3
Depression		10	10	3
Food disorder		10	10	3

TABLE III

Incidence of Different Behavioral Disorders

Disorder	Children (65) aged 2–5 yr.		Children (302) aged 5–15 yr.	
	Number	Per cent	Number	Per cent
Tantrums	35	52	102	34
Extreme nervousness	20	31	132	44
Enuresis and encopresis	20	31	142	47
Aggression	19	29	61	20
Overdemanding	18	28	60	19
Negativism	16	25	84	28
Sleep disorders	14	22	90	30
Food disorders	14	22	30	10
Speech disorders	12	18	57	19
Thumb sucking, nail biting	11	17	33	11
Jealousy	10	15	30	10
Movement disorders	10	15	74	24
Breath-holding	2	3	—	—
Pica	1	2	—	—
Extremely sensitive			78	26
Asocial			64	21
"Nervous pains"			48	16
Antischool			48	16
Loneliness			40	13
Sense of inadequacy			36	12
Lying			33	11
Stealing			30	10
Inordinate ambition			25	8
Truancy			15	5

portance of these factors were arrived at after interviewing the mother or father or both parents, and in the case of older children, after talking with the child sometimes alone, but always on some occasion in the presence of the mother or father. Subject to the parents' agreement, informal contact was made with schoolteachers, medical officers, and health visitors when it was considered that such contact would help. In some cases informal friendly visits to the homes of children were made by the pediatric almoner. On other occasions information concerning the homes of children was obtained from health visitors.

CONTRIBUTORY FACTORS

The factors that were considered to contribute to, and in some cases cause, the emotional disorders are summarized in table IV. The great majority of these factors were related to the child's home environment.

In any one household the child with evidence of emotional disorders was without exception subject to the influence of many contributory disturbing factors. The effect of these factors varied in their impact on the individual child and on different children in the same family. In some children they were the precipitating cause, and in

others only a predisposing cause, of the emotional disturbance. In still others the cumulative effects of environmental conditions and human relationships in the home were both predisposing and precipitating. Table IV does not differentiate contributory factors according to the nature of their impact on the child because management was aimed at offsetting all detrimental influences both within and without the home.

Human Relationships in the Home. There was a high incidence of "absence of the father" and of "maternal exhaustion." The two occurred together with striking frequency. Absence of the father implies that the father was unable to give time to his family because of frequent or prolonged absence from home or because of the demands of night work or regular overtime work. The term "maternal exhaustion" applies to mothers who were emotionally and physically exhausted as a result of disease, rapid childbearing, domestic anxieties, loneliness, or employment additional to bringing up a growing family. Tiredness of the mother led to irritability, ineffective parental control followed. Absence of her husband often contributed to lack of confidence on the part of the mother. In such circumstances the children frequently developed behavioral disorders.

With regard to housing conditions, a state of overcrowding was of particular sig-

TABLE IV

Background Factors: Contributory and Precipitating

Background factor	Children (65) aged 2–5 yr.		Children (302) aged 5–15 yr.	
	Number	Per cent	Number	Per cent
Exacting, inconsistent discipline	33	50	45	15
Rejection, ridicule	18	28	85	28
Overindulgence, overprotection	21	32	60	20
Displacement, overshadowing	10	15	46	15
Alienation of loyalty	2	3	20	7
Domestic tension	14	22	69	23
Bereavement	2	3	27	9
Housing conditions	5	8	30	10
Economic anxiety	3	4	30	10
Maternal exhaustion	11	17	140	46
Absence of father	17	26	103	34
Morbidity in home	3	4	13	4
Interracial marriage	5	8	9	3
Disregarding true age	9	14	19	6
Changes of domicile, school	5	8	13	4
Scholastic pressure			16	5
Teacher, relative: excess emotionalism	3	4	29	10
Professional indiscretion			10	3
Hospital influence	2	3	8	3
Geriatric influence in home	5	8	7	2
Deaf, blind parents	6	9	2	
Twins	2	3	6	2
Divorce court "ward"			4	1

nificance. The constant near presence of too many adults, all possessed of authority, was a cause of confusion and uncertainty in the child's mind and undermined his natural loyalty to his parents. In a multitude of ways and for a multitude of reasons, possessive, exacting grandparents and mischievous and vindictive neighbors were known both intentionally and unintentionally to antagonize a child in his attitude toward his mother. Another finding of importance was the threat to the emotional well-being of the child of overcrowding due to a house being shared by more than two generations. This was particularly noticeable where overcrowding brought the child into constant intimate contact with aged relatives or lodgers manifesting signs of irreversible physical or mental decline. Disturbance of the child was frequently encountered in such circumstances and was profoundly aggravated in the event of the death of an elderly relative to whom the child had been intensely attached.

In a limited number of cases there was clear evidence of the disadvantages to the child of restrictions due to living in furnished rooms, in apartments with difficult access to playgrounds, and in houses adjoining busy traffic thoroughfares.

Poverty per se rarely contributed directly or indirectly to the emotional disturbances in this series. When operative, poverty was usually a measure of unwise, ignorant, or profligate spending of a reasonably adequate income. Overindulgence, and in particular overindulgence that attached prime importance to material values, was a much more common source of trouble than poverty. Material overindulgence on an overwhelming scale was frequently resorted to by parents as a salve to their own conscience, as an antidote to previous irrationally harsh discipline, and to quiet the unruly and to appease the rebellious child. The early ascendancy of material considerations in the outlook and demands of even the very young child was one of the most disturbing findings.

Rejection and Ridicule. These are experiences in childhood that can be of profound and long-lasting significance. Ridicule may arise from the bitterness of a parent conscious of his own inadequacy or disappointed in his offspring. The sarcasm of an exasperated teacher or the sneering of a bullying classmate are other forms of ridicule. Parent and teacher can appear to ridicule by deliberately comparing a child unfavorably with a brother or sister. There were examples of all these in the present series. The children most bitterly conscious of rejection were those unwanted because born out of wedlock or whose mothers were anxious to resume their premarital careers. Several mothers admitted to having lost interest in their children after the stage of babyhood had been passed. There were instances of intolerant stepfathers violently disowning relationship and responsibility in front of the child. In all these circumstances the children knew the bitterness of real rejection. Some children interpreted disinterest in their fun, games, and school activities on the part of parents as rejection, and others felt unwanted when lodged with neighbors while their parents went to work or when banished out of doors or upstairs to preserve quiet for adults in the household.

"Insecurity" the Implications. It is customary to describe emotional disorders in children who have known the hurt of ridicule, rejection, and disturbed human relations as evidence of "insecurity." The term "insecurity" is a cold technical term and conveys little if anything of the utter loneliness and terrifying bewilderment

underlying it. To dispel insecurity we must feel this loneliness and this bewilderment as the child feels them. The need is to consider what bewilderment and loneliness entail for the adult—and then to think of the impact of bewilderment and loneliness on the child with his inherent trust of home and of those in his home.

There were many broken homes in the present series. Insofar as the child is concerned, the term "broken home" does not apply only to those homes where there has been divorce or desertion. It applies equally to homes where there is constant strife, repeated brawling, ceaseless altercation, or unrelieved tension from whatever cause. In such an environment the youngest of children, even although the objects of genuine affection, knew loneliness, bewilderment, and fear—and became the victims of emotional and behavioral disorders.

Physical Stature and Emotional Development. It is customary to think of a child in terms of actual age, intellectual age, and emotional age. Disorders may appear when emotional development is slower than that of actual age. There is another important consideration. Some children acquire a physical stature considerably in advance of the normal for their age. These children are very likely to be urged to social, scholastic, and athletic attainments out of keeping with their healthy chronological intellectual and emotional development. This situation contributed to a number of emotional disorders in the present series. Sometimes it was the attitude in the home, at other times the attitude in the school, that needed adjustment.

Home, School, and Hospital. To many children a change of class or school involving a change of teacher or classmates was deeply if only temporarily disturbing. As to the influence of the teacher, a number of children were bewildered to the point of being frightened when discipline was dependent on noisy correction betraying intense emotion. Discipline and punishment administered with justice and without emotion rarely contributed to insecurity, but undisguised habitual emotional exasperation on the part of parent or teacher readily did so. This view was shared by a number of school teachers with whom it was discussed. A thoughtless attitude toward children on the part of physicians and nurses in hospital or at a clinic has the same effect. The nurse and physician can unintentionally discourage by some ill-considered or ill-timed remark. It is not an altogether uncommon experience for enuretic children, happily conscious of progress, to have a relapse as a direct result of being brusquely asked about their symptoms in the presence of companions.

While treatment in hospital can give rise to emotional disorders, ill-considered publicized generalizations have encouraged exaggerated estimates of the risks. In the present series the risks involved were related primarily to the circumstances necessitating attendance or admission. Thus it was found that a child admitted as an emergency after a frightening accident or a burn was more likely to have emotional disturbance than the child admitted to a medical ward. Of the 16 children (table IV) with emotional disorders contributed to by hospital influences, 14 had received treatment as inpatients and 2 as outpatients. Difficulties in inducing general anesthesia were a feature in 2 cases. Study of several cases emphasized the importance of preoperative preparation not being too obtrusive. It is necessary to stress that the present series does not include children who had had experience of a long stay in hospitals or hospital schools.

TABLE V

Place in Family

Age group, yr.	Place in Family		
	First	Intermediate	Last of several
2–5	32*	11	22
5–15	182†	30	90

* Includes 21 "only" children.

† Includes 66 "only" children.

The Significance of Other Influences. There were several instances of twins presenting their own special problems—more especially where one of the twins compared unfavorably with the other in scholastic or athletic ability, appearance or personality. Several examples were encountered of a deep sense of inadequacy arising in a twin child having to wear spectacles, the other child having no visual handicap. Interracial marriages were a feature of the background in a number of cases—parents of Latin, Teutonic, and Slavonic origin being involved. Detrimental effects on the children involved could be traced to language difficulties and to contrasting parental temperaments. Difference in the religious denomination of the parents, although commonly encountered, was only rarely a source of trouble.

No evidence was found to suggest that extreme youth or elderliness of the parents was a factor of general importance. On the other hand, a significant proportion of children who were very much younger than their nearest siblings experienced emotional difficulties. As to place in the family, findings in the series suggested that disorders were more likely to occur in first children but that this was not accounted for by any marked proneness on the part of only children (table V).

Of the 367 children only 22 had been born prematurely (table VI).

Two situations call for special mention. First, there is the position of children whose parents are divorced and who, living with one parent, are required by order of the court to be seen by the other parent at intervals. Where these circumstances were encountered, the emotional disorders in the children were both fostered and sustained by the unnatural relationships involved. The second situation is mentioned even though the children concerned have been excluded from this survey. The children are those with a parent receiving inpatient treatment at a mental hospital. Nothing was more conducive to perpetuation of emotional disorders in these

TABLE VI

Estimated Gestation Period

Age group, yr.	Estimated gestation period, wk.		
	<38	38–41	>41
2–5	6	58	1
5–15	16	281	5

children than visits paid by them to their parent in hospital or visits made to the children's home by the parent when on parole from hospital.

OUTLINE OF PEDIATRIC MANAGEMENT

General Principles. The fundamental motives underlying pediatric care are the promotion of happiness within the family and the promotion of the total well-being of individuals in the family. Implied in this outlook is the bringing of relief to those with evidence of physical or emotional disorder or pain.

Against this background of approach the aims of management in the present series were to rehabilitate the child and, where necessary, the family; to restore the confidence of the child in his family and of the family in their child; and to correct influences from within and without the family operating detrimentally on the child. An essential of management was unremitting, close cooperation with the pediatric almoner and the family physician. The policy was adopted of "hastening slowly" unless an urgent situation presented. Equally important was the need not to withdraw supportive aid and active personal interest too soon or too suddenly. Children and their parents were seen at intervals ranging from two weeks to three months over a period of one to five years. As improvement became evident, consultations were reduced in length but not at first in frequency. The aim was to maintain continuing personal contact.

Children and parents were encouraged to regard consultations as meetings between friends and to see in the physician a friend as interested and as anxious in the results of treatment as they themselves were. Discussion of his troubles with the child himself was reduced to a minimum. On the other hand, he was encouraged to regard the physician as someone he could talk to about his school, home, hobbies, and athletics and as someone with whom he could share his successes, failures, excitements, and aspirations. As the need for frequent consultations became less, contact was often maintained by letters telling of more achievements and excitements. Slipped into the context of many of these letters were assurances that the writer was now behaving or that his parents were now pleased. Sometimes there was just a cryptic but none the less pregnant sentence to the effect, "Don't worry any more." All letters were answered.

The Parents and the Child. The general principles adopted in approaching the problem of emotional or behavioral disorders are summarized as follows: In conjunction with the family doctor secure the child's co-operation; win the support of the family and household; enlist the help and cooperation of infant welfare and school health services, voluntary organizations, ancillary specialists, and private individuals; and maintain a continuing personal interest in the patient and his family. The approach was empirical and did not deal with the psychology of the disorders.

According to the age of the child and the nature of his problem, the approach to the child and family differed in the individual case (table VII). In the case of some of the older children it was sufficient and indeed better to talk matters over with the boy or girl without going into details with the parents. By this means the child's

TABLE VII

The Child and the Family: Action Taken

Action	No. of children
Direct appeal to the child only	18
Reassurance of family (and child)	15
Adjustments within the family only	51
Adjustments within the family together with direct appeal to the child	36
Support of the family in special circumstances	162

confidence was won and his sense of responsibility recognized. Nothing was better calculated to promote improvement than early expression of an honest conviction that difficulties would be overcome. Reassurance of the child and parent, separately and together, formed the basis of treatment when it was considered that reassurance could be confidently and honestly given. When unqualified reassurance could not be given, the child was encouraged to accept the challenge and the parents to show understanding, to conceal their apprehension, and to contribute to an atmosphere of constructive optimism.

Repeated reassurance coupled with expressed appreciation was sometimes all that was required. In a number of instances, mainly with younger children, the child was not brought into any discussion. Approach to the parents was directed toward encouraging adjustments within the family to remove influences acting detrimentally on the child. There were other occasions when use was made of forms of help forthcoming from outside the family. Invariably parents were given an explanation of the factors thought to be contributing to their child's behavior, the utmost care being taken not to convey any impression of criticism. An encouraging feature was the unexpected frequency with which the full cooperation of the father was obtained when, after previous consultation with the mother, the position was discussed with him. Where older children were concerned, an appeal was often made to them to make their contribution but only after a simple explanation had been given to them of what had been asked of the parents and other members of the family.

Practical Supportive Assistance. In more than 50 per cent of the cases in the complete series, special circumstances pointed to the need of practical supportive assistance of some kind. The forms of supportive assistance are summarized in table VIII. Financial aid was very rarely given. The circumstances warranting it usually arose from sudden desertion of a family by the father, and the assistance given aimed at tiding over a temporary emergency. In a few cases the cooperation of employers and factory welfare officers was enlisted to secure desirable changes in the hours of work of mothers or fathers not involving loss of income. Without exception, employers and welfare officers gave sympathetic hearing to requests put to them. Where loneliness of the mother from whatever cause was a feature of family life, it was often possible to ease the situation by stimulating interest and understanding among friendly relatives and neighbors and by encouraging association with organizations and other community activities.

TABLE VIII

Supportive Assistance of the Family in Special Circumstances

Assistance	No. of children
Holidays for mother and/or child	53
Companionship for child and/or mother	57
Cooperation of relatives, neighbors, employers	25
Adjustments in father's or mother's employment	15
Improved housing conditions	6
Financial	6

There were many examples of children lacking companionship of appropriate age. Here again help on behalf of the child and mother was often obtained from relatives, neighbors, and organizations. Supportive assistance given consisted frequently of no more than explaining the need and providing initiative. Where exhaustion of the mother or child or both was a major feature, recourse was often had to arranging a country or seaside holiday removed from home surroundings in need of stabilization. The circumstances of the individual case determined whether the mother, the child, or both were given a holiday. Several instances of long-standing, intense mutual antagonism between a completely exhausted mother and her aggressively negativistic young child were effectively dealt with by separation of the mother and child for several months. Whenever possible the child was sent for a holiday with relatives to whom the situation was explained and who had children of their own. During the time of separation the mother was persuaded to rest and helped to reacquire confidence, and the opportunity was taken with the aid of the family physician to secure necessary adjustments in the home before the child's return.

The Contribution of the Infant Welfare and School Health Services. Supportive assistance was often dependent on help from other sources. Table IX indicates the generous help received from the infant welfare and school health services. Ample evidence was obtained of the therapeutic value to emotionally disturbed younger children of understanding care in a day nursery. Children who derived benefit were those

TABLE IX

Assistance Secured from the Infant Welfare and School Health Services

Nature of assistance	No. of children
Enrollment in day nursery, nursery school	24
Accelerated enrollment at elementary school	9
Change of school or class	42
Discussions with school medical officers and teachers	74
Admission to special school for handicapped children	38
Services of health visitors and/or "baby sitters"	15

TABLE X

Assistance from Voluntary Organizations, Officers, Private Individuals

Source of assistance	No. of children
Youth organization	36
Youth employment officer	6
University Institute of Education	9
Psychiatrist	10
Speech therapist	28
Minister of religion	5
Probation officer	8

bereft of child companionship, those who lived in crowded apartments, and those deprived of their mother during the day. Where a nursery or nursery school was not available, agreement to advancement by a few months of the time of enrollment at the elementary school was obtained. This is not a policy for general application but was of value in the carefully selected case. Other help received from the infant welfare services included arrangements for visits by health visitors and for "baby sitters," enabling father and mother to enjoy an occasional evening out together, confident that their children were in safe keeping.

With regard to children of school age, discussions with teachers frequently facilitated and accelerated treatment by filling gaps in our knowledge or confirming impressions arrived at previously. The most convincing proof of the value of this cooperation between physician, teacher, and administrator is that there was rarely disagreement concerning the desirability of a child's class or school being changed.

The Contributions of Voluntary Organizations and Private Individuals. Help of a different kind and of endless variety was received from many organizations and their officers and from a number of private individuals (table X). Great assistance was obtained from youth clubs, boys' clubs, and girls' clubs. Many children were encouraged to join the Boy Scouts, the Sea Scouts, or the Girl Guides. A practice was made of speaking to the youth leaders personally, and they invariably responded by taking a keen personal interest in the new recruits sent to them. Ministers of religion gave similar help in connection with children attending their churches, Sunday schools, or church clubs. In a few particularly difficult cases, colleagues at the University Institute of Education interviewed pupils from preparatory or public schools (together with their parents) and gave invaluable advice. Help of a different kind was received concerning vocational guidance and supervision for selected children from the youth employment officer and the probation officer. Great assistance was obtained from speech therapists where required and a psychiatric opinion was secured in the case of several adolescents.

In reality the lines of management were essentially simple. There was no elaborate pharmacy and no rigid professionalism. Basically the relations established between the patient and family on the one hand and the almoner and physicians on the other consisted essentially of trust, understanding, and common sense. The help provided aimed at explaining and removing the causes of trouble and at bringing confidence

and support to the family until time and nature brought about improvement or cure. Account and advantage were taken of the trend to normality, which is favored by development and maturation in the individual.

THE RESULTS

The 367 children in the series were followed up for periods varying from two to eight years.

Complete failure has to be admitted in connection with 38 children. An attempt has been made to unmask the reasons for failure in each case, and these are given in table XI. Conclusions concerning mental deficiency and educational subnormality were confirmed by colleagues in the school health service. Superficially the reasons listed in table XI appear to attribute blame to the child or the family. Another major factor contributing to failure in the management of each of these cases was my own variable inadequacy. In these particular cases this inadequacy took the form of inability to promote or establish the essential, no matter how intangible, sense of mutual interest and confidence with the child or family. Children who failed to respond and who, from the point of view of this study, were complete failures were those manifesting delinquent tendencies, stealing, extravagant lying, and truancy. The age of the majority of these children was 11 years or more. Five of these children are known to have been diagnosed at a later age as being psychopaths. It is probable that the abnormal behavior of others in this group was evidence of congenital instability of mind. Not a few of these children were members of "gangs" and others were under the influence of older juvenile criminals. One or two were younger but, in general, delinquent trends in those less than 11 years old were not resistant to pediatric management.

Follow-up of the remaining 329 children justified the conclusion that treatment had been beneficial. The word "beneficial" is used deliberately because it is not possible to assess the results of treatment reliably in such relative terms as "improvement" or "cure." Considerations of the child and considerations of the child's family were inseparable. For this reason, results evaluated according to whether the child's disorders were benefited and whether adjustment of the family was assisted are given in table XII. Assessments of failure or benefit are based in each

TABLE XI

Factors Limiting the Effectiveness of Pediatric Management (38 Complete Failures)

Factor	No. of children
Mental deficiency	7
Educational subnormality	7
Family unwilling to cooperate	8
Family willing but unable to cooperate	3
Family cooperation erratic	4
Irremediable background	5
Cooperation of child not secured	4

TABLE XII

Pediatric Management of Severe Behavioral Disorders: Assessment of Results

Children		Relief of the child's disorders	Adjustment of the family
Age, yr.	Number		
2–5	12	Considerable	Complete
(65)	53	Complete	Complete
5–13	13	None	None
	17	None	Considerable
(268)	89	Considerable	Considerable
	149	Complete	Complete
13–15	5	None	None
(34)	3	None	Considerable
	26	Complete	Complete

case on a correlation of the information volunteered by parents, the opinions of the family physician, and personal observations and conclusions arrived at by my almoner colleague and myself.

CONCLUSION

Emotional and behavioral disorders in children constitute a major problem in social pediatrics. The children included in the present study were with few exceptions the victims of disturbed human relationships and of abnormal home environment. The problems the children presented were attributable to the wider problems of society. Genetic influences, which were not considered in the present study, may have been operative in some cases. The influence of ignorance, housing conditions, industrialization, conditions of employment, and moral standards was everywhere evident. Beneficial treatment was made possible only by marshaling and co-ordinating the experienced knowledge of professional and lay workers, of workers in and out of hospital, of state and voluntary organizations and of parents, relatives, and neighbors. Treatment was erected on a structure of integrated team work. In this complicated approach the children's physician is in a position to preserve perspective — to seek specialist aid where it is required but always to preserve the conception of the child as an individual within the sanctity of the home.

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Kenny Foundation Scholarships

The Sister Elizabeth Kenny Foundation announces continuation of its program of postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases. The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5000 to $7000 a year, depending on the scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible. Inquiries about the scholarships should be addressed to Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, 2400 Foshay Tower, Minneapolis 2, Minn.

A Combined Psychic and Somatic Stimulant in the Management of Industrial Fatigue and Mild Depression

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In industrial medicine, the management of the ambulatory patient with fatigue and depression, of necessity, has to depend more on psychopharmacology than on psychotherapy. The extensive use of psychological approaches is desirable, but unfortunately not feasible. The care of older employees particularly often calls for the use of medication to stimulate mental alertness and combat physical fatigue. Proper selection of such therapy will help provide the patient with a larger span of usefulness to himself as well as to industry.

Central nervous system stimulants are characterized by a narrow border between the optimal therapeutic dose and the onset of undesirable side effects. This obstacle to satisfactory management aroused our interest in a new combined form of stimulant medication* intended to meet this objection. Three structurally dissimilar cerebral stimulants with overlapping clinical effects were combined, employing smaller amounts of each, with the aim of reducing the incidence of side effects without interfering with the desired therapeutic action. The three components were selected in such a way as to provide an additional benefit, a wider therapeutic range permitting the alleviation of a broad spectrum of psychic and somatic symptoms.

The somatic effects of even mild depressions are being more generally appreciated, due especially to the demonstration and measurement by Funkenstein[5] of the disturbances in cardiovascular function characteristic of these patients. Many common symptoms are now considered often to represent direct equivalents of depression. These include functional upper gastrointestinal disturbances,[1] anorexia and fatigue,[7] headaches of the muscular and vascular type, and a large variety of ill-defined pains and weaknesses.[2] Thorner[10] pointed out that unhappy and depressed persons tend to suffer from insomnia, constipation, hypertension and tachycardia, a decreased appetite, and reduced libido and that their skin tends to be cold and their fingers and toes often cyanotic. He does not accept the widely held view that depression is responsible for loss of energy and the other symptoms just listed but suggests that the very constant association between them may be due to some deranged physiological process resulting in these far-flung abnormalities. In the older age group, the tendency to react with somatic symptoms to depressing situations is especially pronounced.[13]

* The trade name of G. F. Harvey Co., Inc., for a new combined form of stimulant medication is Dexazyme. The formulation per capsule is: d-amphetamine sulfate, 3.0 mg.; pentylenetetrazol, 130.0 mg.; niacin, 50.0 mg.; thiamine hydrochloride, 5.0 mg.; riboflavin, 2.0 mg.; ascorbic acid, 37.5 mg. The drug was kindly furnished for this study by the Medical Department of G. F. Harvey Co., Inc.

The three analeptic components of the stimulant medication used in this study are d-amphetamine sulfate, pentylenetetrazol, and niacin. The amphetamines are generally considered the euphoriants of choice—they stimulate activity of the central nervous system as well as of peripheral tissues, assist in the integration of reflex or automatic behavior, lift the patient's mood, and help dispel his discomforts. The only major failing is a marked and completely unexplainable variability of action[16] in different individuals.

Pentylenetetrazol is an effective and safe analeptic, especially in the older patient. It has been found of particular value in the treatment of mental disturbances associated with senility,[10] the patients becoming more perceptive, alert, pleasant, and cooperative and less agitated with its use. The dosage of pentylenetetrazol should be kept low, as nausea and vomiting are encountered with larger dosages.[1] The drug does not lead, however, to blood pressure rises and even serves to decrease arterial pressure in cases of hypertension.[8]

The role of niacin is that of a cerebral vasodilator. Its action may be expected to be particularly valuable in the elderly person, whose cerebral circulation is characterized[6] by a decrease in blood flow, a decrease in metabolic rate, and an increase in vascular resistance. The high metabolic activity of the brain and its extreme dependence on circulating oxygen, carbohydrates, and other circulating metabolites make it unusually susceptible to even mild ischemia. The cerebral circulation does possess compensatory mechanisms to protect it against fluctuations in the supply of these materials, but when these mechanisms become inadequate, functional disturbances and structural damage rapidly result. When used in combination with pentylenetetrazol, niacin has been shown to be effective, safe, and free from side effects[11, 14] and particularly helpful in those patients with only mild memory difficulties, in the absence of more serious emotional and psychiatric disturbances.

In addition to these three analeptic agents, the combination stimulant contains three vitamins, thiamine hydrochloride, riboflavin, and ascorbic acid, which are concerned with carbohydrate metabolism and, therefore, are important to the cerebral circulation.[6]

METHOD

The preparation under study was administered for periods ranging from 1 to 12 weeks to 63 patients seen both in a geographically far-flung industrial practice (including retired workers) and in medical office practice.

The patients were divided into two groups: one, middle-aged patients with fatigue and depression, and the other, senile patients, most of whom suffered either from arteriosclerosis, hypertension, or a combination of the two.

Forty-two patients fell within the middle-aged group, with an average age of 46 years. The chief complaints were fatigue, lassitude, anxiety, and depression. Organic disease had been carefully ruled out. All the complaints gave evidence to the examining physician of being psychosomatic in nature and accompanied by neurosis of a mild or moderate degree.

The second group consisted of 21 patients with an average age of 67 years. The characteristic diagnosis in this group was senility, and the chief complaint in the

TABLE I

Symptoms at First Visit

Symptom	Group 1 (middle-aged)	Group 2 (elderly and senile)
Fatigue	22	8
Lassitude	17	9
Depression	8	6
Anxiety	5	3
Memory lapses	0	15
Dizziness	1	7
Vague pain	9	5
	62	53
Number of patients	42	21

majority of cases was loss of memory, especially of recent events. While numerous complaints of depression, fatigue, and anxiety were also present, they appeared to be dominated by the cerebral manifestations of arteriosclerosis and hypertension. The psychosomatic overlay was of little importance in this group. Multiplicity of symptoms was an outstanding characteristic of this group, 53 major complaints being recorded for only 21 persons. (Table I.)

Most of the patients in group 1 had specifically requested antidepressant medication in the dispensary prior to their examination by the physician, while most of the patients in group 2 were started on such medication when depression was found to be a major element in their state of ill health, either during medical treatment or in the course of a periodic or retirement examination.

The dosage of the combination stimulant administered to our patients was 1 capsule twice to three times daily with adjustments to optimum dosage as needed. In each case, the starting dosage consisted of 1 capsule three times daily, taken in the morning, at noon, and in the middle of the afternoon.

The course of the patient during the period of treatment was graded as improved, unimproved, or worse. Pulse and blood pressure were taken and recorded weekly in order to detect any abnormalities.

RESULTS

The summary of results in table II indicates that 76.2 per cent of all patients in this series derived benefit from the use of this medication. The response to the combination stimulant among the elderly and senile patients was excellent. Of a total of 21 patients, 18 (86 per cent) were made considerably more comfortable, and their symptoms were markedly reduced. Thirty of the 42 younger patients (71 per cent) derived benefit from this course of treatment. As a rule, this improvement extended to all of the major symptoms present initially to about the same extent. Selective action, with improvement of some but not of other symptoms, was not noted. The patients felt more able to engage in and less tired after performing their assignments, a general lifting of mood alleviated both depression and anxiety, and ill-defined

TABLE II
Results of Treatment

	Number of patients	Improved	Unimproved	Worse
Group 1	42	30	10	2
Group 2	21	18	2	1
Total	63	48	12	3

pains either disappeared or became more amenable to minimal analgesic therapy. Patients reported less apathy, less vagueness, and improved ability to concentrate, all of which served to bring about a noticeable increase in working efficiency among our employee patients.

As could have been expected, the most common side effect of niacin in this combination was marked but transient flushing, itching, and tingling of the face and upper trunk. The cutaneous vasodilatation brought about by niacin was greater than that which we have in the past encountered with equal dosages of niacin alone, so that apparently this effect may be enhanced by its combination with the other active ingredients. Other side reactions of this preparation were insomnia, which occurred in 13 of the 63 patients, and nausea, which caused discontinuance of therapy in 2 of 7 instances.

In the younger patients (group 1), the side effects were such as to warrant discontinuance in 26 patients. In the older patients (group 2) blushing was as common, but it was accepted by the patients both because of the concomitant relief of symptoms and because it gave them a comfortable sensation of warmth. Therapy could

TABLE III
Number of Side Effects

Side effect	Number of patients
Flushing	17
Insomnia	13
Anxiety and nervousness	9
Nausea	7
Tremors	3
Headache	2
Hyperhidrosis	2
Palpitation	1
	54 in 33 persons

Total number of patients: 63.
Number of patients reporting side effects: 33.
Total number of individual occurrences: 54.
A number of these side effects cleared up on reducing dosage to 2 capsules daily, while others tended to disappear with continued administration.

be completed in all but 2 of the 21 patients in this group. It should be noted that the flushing due to much larger dosages of niacin has been shown to subside after four to seven days of therapy.[12]

DISCUSSION

It is in the older patient that the results are promising. These patients are improved sufficiently by the combination stimulant to overlook any possible unpleasant side effect in order to obtain improvement of mental and emotional faculties. We feel that in the younger employee or patient, the use of this drug combination for the treatment of psychosomatic complaints is undesirable. In those patients who did not discontinue therapy because of undesirable side effects, the results were not particularly better than those that can be obtained with a single euphoriant.

In this age of increasing emphasis on employment of the older worker, a drug or combination of drugs to improve his mental processes and work capacity is well worth searching for. In the older age groups, the importance of weariness and boredom in accelerating deterioration of the body must be kept in mind. Bortz[2] has recently re-emphasized that loss of the body's ability to adapt to external stresses is an important concomitant of the aging process. This situation, as applied to industrial practice, can be visualized as a vicious cycle: weariness and fatigue lead to deterioration of mental and somatic abilities and to inefficient functioning on the job, which in turn further aggravates fatigue and other depressive symptoms.

In the majority of patients in this series, a four- or five-week course of therapy with the combination stimulant was followed by relief from fatigue, weakness, and depression. It is of great interest that 16 patients maintained their improvement after removal of medication, while 7 relapsed. The fact that this type of favorable response was so much more frequent in older patients further emphasizes the need for active therapy and the futility of a *laissez faire* approach.

In this connection, it should be pointed out that, in spite of a widely held false belief, the work experience of the older group is not necessarily worse than that of the younger. Older workers compensate[9] for their relatively greater fatigability, irritability, and lack of adaptability by reduced absenteeism and greater experience and interest. It is our impression that, with the occasional employment of the proper stimulant medication when indicated, the production records of older persons may reasonably be expected to equal those of younger employees.

SUMMARY

Sixty-three fatigued, depressed, or elderly ambulatory patients were treated with a new stimulant formulation containing d-amphetamine sulfate, pentylenetetrazol, and niacin.

Excellent results were obtained in the elderly group, with marked improvement in powers of concentration, increased working efficiency, and less complaints of fatigue and depression. The drug does not appear as useful in the younger adult, in whom side reactions appeared frequently enough to detract from such beneficial effects as were obtained.

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Health Survey of School Children

The Public Health Service has embarked on an exploratory program with 40,000 children in Chicago's elementary schools to ascertain whether the electronic recording of heart sounds can be used as a mass screening method for finding individuals with cardiac lesions who are in need of medical attention. The pilot study will take 18 months.

The Pharmacology of the Psychotomimetic Agents

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The changing pattern of our picture of mental disease is reflected in the character of the Symposium on the Chemical Concepts of Psychosis, which was held at the Second International Congress of Psychiatry in Zurich in 1957. Illustrious scientists from many disciplines throughout the world are focusing their attention on the recent advances in chemistry as these are related to mental illness. If the interpretation is correct, these developments herald novel and significant discoveries in the near future. Perhaps the most provocative discovery in this area in the past few years has been the finding of a number of chemically unrelated substances that selectively produce psychotic-like changes in thought, mood, and perception. These chemicals have been termed "psychotomimetic" or "psychotodysleptic" agents.

The psychotomimetic agents are potentially useful in inducing experimental psychoses in man. In addition, it has been postulated by some workers that certain of these compounds may be involved in some forms of mental disease. Some of these substances produce aberrant behavior in animals. As a group they produce their unique mental effects largely divorced from any profound physiological changes. The psychiatrist is interested in the psychotomimetics because they mimic to some degree, usually limited, the state of mental illness in man. In the literature these states have been termed the "model psychoses," although there are a number of objections to the use of this phrase in this manner.

Osmond[1] has offered a generalized description of this class of compounds: "Psychotomimetic agents," he stated, "are substances that produce changes in thought, perception, mood and, sometimes, in posture, occurring alone or in concert, without causing either major disturbances of the autonomic nervous system or addictive craving, and although, with overdosage, disorientation, memory disturbance, stupor, and even narcosis may occur, these reactions are not characteristic." The following classification of the psychotomimetics has been proposed by Kline:[2]

a. Hallucinogens: producers of hallucinations (auditory, visual, sensory, etc.).
b. Cataleptogenics: producers of rigid or unresponsive conditions in which the subject does not respond to stimuli although he is fully conscious and in no sense comatose.
c. Euphoriants: agents which elevate mood to an abnormal degree.
d. Chronoleptogenics: drugs which distort the sense of time.
e. Depressants: agents which lead to an abnormally "low" mood or emotional status.
f. Disinhibitors: compounds which remove the normal and customary inhibitions in respect to speech, fantasy, feeling and/or action.
g. Confusants: preparations which induce in the subject a state of perplexity and/or confusion.

Delay[24] has proposed the term "psychodysleptic" to describe all substances that induce delusional aberration of judgment with a distortion of the appreciation of reality.

In describing the effects of psychotomimetic agents, observers have not differentiated the actions on subjects in terms of this classification. In fact, most of the agents produce many effects and there is no sharp distinction between those that induce confusion or depression or hallucinations, for example. At the present time the category is broadly conceived and the scope of the subject for this review is described in the following section.

Our knowledge about psychotomimetic agents rests largely on the empirical experiences, taboos, religious rituals, and medical practice of many tribes and peoples over the face of the earth. The bibliography of this subject ranges from reports of explorers into the little-known regions of the world, to studies of anthropologists and psychologists on the mores and behavior of primitive people, as well as careful scientific evaluations of the effects of plant and animal drugs and synthetic chemical compounds on man and animals.

Psychopharmacological investigation of the many compounds that produce mental effects has only recently been attempted. This was stimulated by two approximately simultaneous events: the discovery of the clinical usefulness of the ataractic drugs and the announcement of Hofmann's astonishing substance, lysergic acid diethylamide (LSD). It is true that the history of mankind is rich in the lore of, and intimately entwined with, the use of many substances that produce strange effects on the mind. But these observations in history have remained largely unexplored. However, recently many provocative leads have been uncovered and gradually a position favoring a more logical approach to the study of psychotogens is emerging. Now, based on the known chemical structure of active hallucinogens, we are beginning to synthesize and study homologues and analogues. The remarkable effects of minute amounts of 50 to 100 γ LSD were accidentally observed by Hofmann on April 16, 1943.[3] This discovery was disclosed in 1947 and it provided a potent stimulus for further exploration of related substances.

PSYCHOCHEMICAL SUBSTANCES

Many chemical substances of known composition have been observed to produce abnormal behavioral effects in animals and man. If one excludes the hypnotic, anesthetic, and convulsant effects of drugs, there remains still a group of symptoms produced by chemical agents that suggest disorientation of normal behavior. This report is concerned with those agents that produce hallucinations and psychotomimetic effects of the type described by Osmond and categorically does not include cocaine, cannabis (marihuana), morphine, barbiturates, amphetamine, or scopolamine. In several publications these well-known drugs have been compared with the psychotomimetic agents in "psychoexploration."

A tabulation of substances known to produce hallucinations, disorientation, and changes in thought, perception, and mood in man is given in table I. By definition, only those substances are included that produce a psychotic-like picture in a high

TABLE I

Compounds Reported to Elicit Psychotomimetic Effects in Man

d-Lysergic acid diethylamide; LSD-25
d-Lysergic acid monoethylamide; LAE-32
d,l-Acetyl-lysergic acid diethylamide; ALD-52
N,N-Dimethyl-5-hydroxy tryptamine; bufotenin
N,N-Dimethyl tryptamine; DMT
(6 Methyl-4,5,pyrido) 2,3)-9 methoxy indole; harmine
2-Diethylaminoethyl cyclopentyl (2-thenyl) glycolate; Win-2299
3,4,5 Trimethoxyphenylethylamine; mescaline
3,4,5 Trimethoxyphenyl-β-aminopropane; trimethoxy amphetamine; 3,4,5, TMA
Oxidation products of adrenaline; adrenochrome, adrenolutin
N-Allylnormorphine; nalorphine
Piperidyl benzilate esters:
  N-Ethyl-3-piperidyl benzilate, JB-318;
  N-Ethyl-3-piperidylcyclopentylphenyl glycolate; Ditran, JB-329
1-(1-Phenylcyclohexyl) piperidine; Sernyl
Ortho-phosphoryl-4-hydroxy-N-dimethyl tryptamine; psilocybin

percentage of subjects. Many drugs occasionally produce bizarre mental symptoms when they are used therapeutically, for example, cortisone. Drugs of this type are not classified as hallucinogens. Wikler[4] has commented on the variability of response to different drugs and the same drug, including hallucinogens, when these agents are given to similar types of patients in standardized observer situations. Relatively few studies have been reported in which different drugs have been compared under identical or even closely similar experimental conditions. Wikler is of the opinion that if more ideal studies were made, a considerable degree of drug specificity would be demonstrated.

The symptoms in animals suggesting hallucinogenic actions as reported by various workers have not been helpful in screening chemical agents for psychotomimetic properties in man. These tests range from behavior observations of fighting fish and many other animals, to learning performance discrimination and measures of locomotor activity in rodents and other species.

LSD and Related Compounds. It is of considerable interest that of 18 chemical compounds, closely related to LSD, that were synthesized by Stoll, Troxler, and Hofmann, only two induced marked psychotic changes in man (fig. 1). These are the acetyl diethylamide (ALD-52) and the monoethylamide (LAE-32) derivatives. The ethyl group in the amide position is particularly important for psychotic effects. The 1-methyl derivative of lysergic acid diethylamide (MLD) has been reported as a weak psychotomimetic. It is striking that of the four possible stereoisomers of LSD only the "d" variety is active as a hallucinogen.[2] Most of these derivatives of lysergic acid have been carefully studied by the workers in the Sandoz Laboratories in Basel, Switzerland.

The acute intravenous toxicity of LSD for the rabbit is very great, the LD_{50} being only 0.3 mg./Kg. There is a wide species variation, however, and the LD_{50} for the mouse and rat is 46 and 16 mg./Kg., respectively. None of the other ergot alkaloids exhibit this high activity. No tolerance appears to develop in the rat on repeated

intravenous administration; however, tachyphylaxis develops in the rabbit. In this respect the rabbit's response resembles that of man.

We are indebted to numerous workers for our knowledge of the metabolic fate of LSD. This literature has recently been reviewed by Rothlin.[5] LSD as the tartrate is well absorbed orally, it passes quickly from the blood to the tissues, the concentration in the brain is always lower than that in the blood, it is found in all organs and is excreted quickly in the bile. Two hours after a single dose, only traces can be found in the blood and organs. LSD passes into the cerebrospinal fluid in measurable amounts. Using C^{14}-labeled LSD it has been found that only very low brain concentrations are required to induce prolonged behavioral changes. The substance is extremely rapidly removed from the brain, and this suggests that behavior changes are due to a reaction sequence, triggered by LSD rather than related to the persistence of the substance in the central nervous system.

The pharmacological effects of LSD and other psychotomimetic agents can be divided into direct peripheral actions and effects on the central nervous system. LSD causes a peripheral vasoconstriction in isolated organs but its centric depression of the vasomotor centers predominates and this produces a fall in blood pressure. Its sympatholytic actions, however, are relatively weak in comparison with those of the other ergot alkaloids. Many of the autonomic effects are manifested as observable peripheral changes; piloerection, mydriasis, salivation, and lachrymation are induced.

LSD induces its most interesting actions on the central nervous system. The agent provokes an increase in body temperature in the cat, dog, and rabbit, while only very high dosages are pyrexic in the rat. Perhaps the most significant centrally induced effect is the action on the temperature-regulating center of the rabbit. Small doses of 0.5 to 1.0 μg/Kg. raise the body temperature significantly. This is an easily

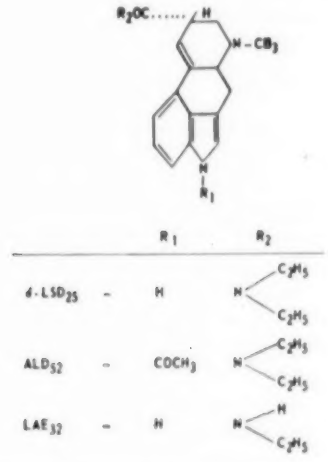


FIG. 1. Structural formulas of active lysergic acid derivatives.

measured, quantifiable change, in an animal, that follows a dosage on a body-weight basis comparable to the dosage of LSD that induces psychotomimetic changes in man. It should be pointed out, however, that this does not imply that hyperpyrexia and psychic changes are necessarily related.

Because LSD produces a very positive psychotic-like state in man, it is of special interest to see how LSD affects behavior in various laboratory animals in experimental situations. The excitatory syndrome in rabbits after intravenous injection is interesting but not unique. LSD produces motor hyperactivity and hyperreflexia. These effects are also produced by other derivatives of lysergic acid, especially ALD-52 and LAE-32, and other drugs.

LSD produces restlessness and excitement when injected intravenously in dogs. However, when the agent is administered chronically, apparently the symptoms subside. In monkeys intravenous injection produces severe visual disturbances, a marked degree of tameness, and some ataxia, but skeletal muscle tone is preserved. Mice respond to intravenous doses of LSD with a peculiar and characteristic head shake that persists for weeks in some animals; intracerebral injection is said to increase aggressiveness in this species. In rats LSD administered intraperitoneally provokes restlessness, head-shaking, flexed legs with crawling motions, and eventually prolonged inactivity. In rats trained to climb a rope, LSD produces signs of confusion and markedly prolongs climbing time. The rope-climbing performance time is linearly related to the log dose of LSD.[6]

A number of rather exotic behavior tests have been devised to demonstrate the hallucinogenic action of LSD, including web-building by spiders, fighting behavior in fish, and disorganized movement in snails. Unfortunately, the usefulness of these methods to detect psychotomimetic action does not appear to parallel the enthusiasm of the researchers intrigued by these test objects.

In general, we can say that LSD in animals behaves like a stimulant drug. Like amphetamine it produces excitation and fast, low-amplitude electrical activity of the brain. It produces its stimulant effects, however, in relatively small doses. Some investigators feel they can detect hallucinations in animals after LSD but this remains a moot question.

A number of workers have attempted to elucidate the action of LSD in man by studying antagonistic agents. Very large dosages of barbiturates or intravenous dextrose will partially combat LSD effects. Chlorpromazine, reserpine, serotonin, and combinations of amobarbital and methamphetamine are reported to be effective antagonists. In addition, nicotinic acid, pipradrol hydrochloride, and azacyclonol hydrochloride will apparently antagonize some effects of LSD. Of interest in this connection is the observation of Ginzel and Mayer-Gross[23] that the 2-brom derivative of LSD, identified as BOL-148, can block the mental disturbances elicited by LSD in normal volunteers. The blocking effect is exerted only if the BOL is administered prior to the LSD. BOL itself exerts no psychological effects. Glutamic and succinic acids are said to terminate the mental symptoms induced by LSD, which suggests that a disturbance in carbohydrate metabolism may be involved. These rather speculative findings have prompted some writers to propose a biochemical foundation for some psychotic-like states.

An excellent description has been given by Rinkel[7] of the mental manifestations elicited by LSD. In general, these resembled the acute schizophrenic turmoil state. Outstanding were the dissociation of thought processes, inappropriate affect, and catatonic features. Depersonalization phenomena were experienced by nonpsychotic subjects relating to their own bodies and to objects and persons in the environment. Disturbances of visual, gustatory, auditory, and tactile perceptions were noted. Hallucinations were not always experienced, although feelings of unreality were common. Intellectual functions were not disturbed and consciousness was not impaired with respect to time, space, and the nature of the experimental setting.

Bufotenin and Related Indole Alkylamines. Bufotenin is N,N-dimethyl-5-hydroxy tryptamine or dimethylserotonin (fig. 2). The alkaloid may be prepared synthetically or extracted from the bean *Piptadenia peregrina*, long known to be the source of an intoxicating "snuff" used by South American Indians. The hallucinogenic properties of this plant alkaloid, its close association to serotonin, and the fact that LSD and serotonin are antagonistic have provoked a considerable body of research. Numerous concepts of altered brain metabolism have been proposed to explain the observed behavioral effects. No explanation seems to be adequate or widely accepted at the present time.

Fabing and Hawkins[8] described the effects of intravenous injections of 8 to 16 mg. of bufotenin in human volunteers as primary visual disturbances, alteration of time and space perception, and paresthesias. The physiological effects of cyanotic flushing (purple hue of the face), nystagmus, mydriasis, and a transient rise in blood pressure are similar to those produced by serotonin, although the latter compound does not elicit hallucinations. Brain hypoxemia must not be overlooked as a possible explanation of the effects of bufotenin. Bufotenin and serotonin are capable of causing powerful constriction of smooth muscle, for example, bronchiolar constriction and chest discomfort, and a selective vascular constriction in some brain regions may be produced by these agents.

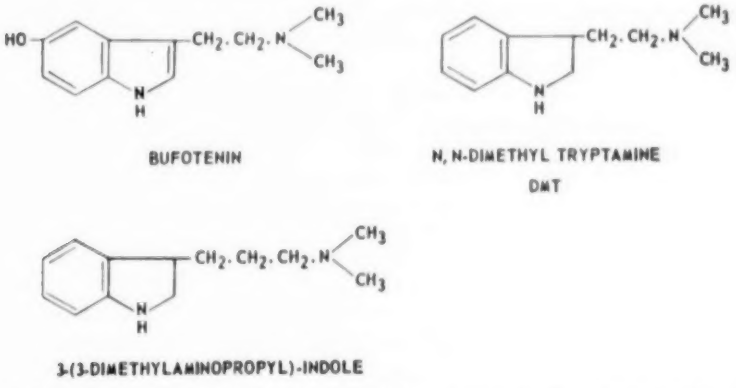


FIG. 2. Structural formulas of bufotenin, N,N-dimethyl tryptamine (DMT), and 3-(3-dimethylaminopropyl)-indole.

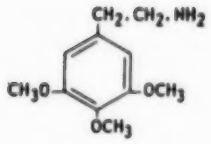
Turner and Merlis[9] gave doses of bufotenin up to 20 mg. intravenously to schizophrenic subjects without observing hallucinations, despite profound electroencephalographic changes, loss of consciousness, and intense serotonin-like peripheral purple skin-color effects. These workers proposed that if a substance were involved metabolically in schizophrenia, then the intravenous injection of that substance might specifically increase the metabolic load and lead to a recrudescence of a psychosis. In other words, they consider the schizophrenic patient a more sensitive test subject. Their argument was strengthened by the subsequent finding that N,N-dimethyl tryptamine (DMT), or bufotenin without the OH group on the ring, did produce psychotic-like states with less intense physiological actions. Specificity of structure was demonstrated by showing that 3-(3-dimethylaminopropyl)-indole was inactive physiologically and did not produce hallucinations or psychological effects in doses up to 70 mg. intramuscularly (fig. 2).

When injected intravenously in the monkey, bufotenin causes symptoms characterized by gross sensory disorders and decreased reaction to pain or visual stimuli, but no loss of skeletal muscle power. The effects resemble those produced by LSD. Initially there is inactivity in the prone position, arm and leg muscles have normal tone, and there is some ataxic circling, which decreases gradually with a loss of response to noxious stimuli and temporary blindness. The degree of tameness permits the experimenter to place his finger in the monkey's mouth with impunity. Auditory or vestibular functions do not seem to be adversely influenced by LSD or bufotenin.[10]

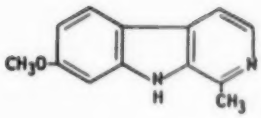
In the rat, bufotenin causes the hind legs to be splayed out in pseudoparaplegic fashion, plus a continuous beating of the forepaws, "as if a virtuoso were attacking a piano fortissimo." In the dog, intravenous injections cause similar hind-leg pseudoparaplegic splaying, salivation, pilomotor effects, and an unearthly, persistent howling. Under the influence of bufotenin the dog is indifferent to noxious stimuli and nondefensive against attack.[8]

Harmine and Substituted Pyrindoles. Harmine is ((6 methyl-4, 5,pyrido)2,3)-9 methoxy indole (fig. 3). It may be prepared synthetically or isolated from the seeds of *Peganum harmala* or the wood of *Banisteriopsis caapi*. A number of closely related compounds, i.e., harmaline (3,4-di-hydroharmine), norharmine, harminic acid, and apoharmine, are also known.

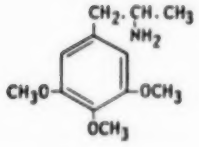
Originally harmine was investigated for its hallucinogenic properties because the various species of *Banisteria* are used by South American natives to prepare decoctions that produce hallucinations and intoxication.[11] Until recently there were no reports of any psychic effects resulting from the administration of harmine, even though the alkaloid has been known and studied for many years. It is a convulsant poison in mice and monkeys. Pennes and Hoch[12] found that the intravenous injection of from 150 to 200 mg. of harmine hydrochloride in schizophrenic patients produced visual hallucinations, humming and buzzing noises, "waviness" of the environment, "sinking" sensations of the body, a subjective sense of body vibration, and numbness with reduced sensitivity to light touch and pinprick. These investigators were unable to elicit hallucinations with harmine by oral or subcutaneous routes. These authors described the effects of harmine, Win-2299, and nalorphine hydrochloride (fig. 4) as grossly similar to those elicited by mescaline and LSD. Unlike the latter



MESCALINE



HARMINE

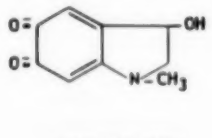


3, 4, 5, TMA

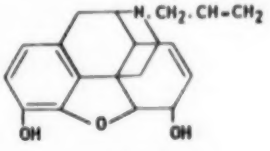
FIG. 3. Structural formulas of mescaline, harmine, and 3,4,5, TMA.

two agents, however, these drugs produced a marked hypnotic effect after the visual hallucination and imagery stage. Pennes and Hoch suggested that differences between all these agents are quantitative rather than qualitative.

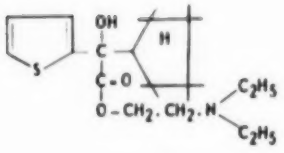
Mescaline and Trimethoxyphenyl Alkylamines. Mescaline is 3,4,5-trimethoxyphenylethylamine (fig. 3). It is found along with other alkaloids in the dumpling cactus *Lophophora williamsii*. This is the peyote or mescal used by North American Indians for religious purposes. In 1898 Heffter reported his own hallucinatory experiences after ingestion of mescaline, and more recently these have been vividly described by Huxley.[12] This psychotomimetic has been known for a long time but it remained largely a psychiatric curiosity until the advent of LSD. Mescaline, like LSD, has



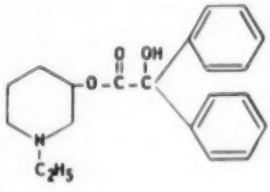
ADRENOCHROME



NALORPHINE



WIN-2299



JB-318

FIG. 4. Structural formulas of adrenochrome, nalorphine, Win-2299, and JB-318.

been used experimentally for diagnostic, prognostic, and therapeutic purposes in schizophrenic patients. An excellent review of the pharmacology and metabolism of mescaline has been prepared by Fischer.[14]

After oral doses of approximately 300 mg., normal subjects develop symptoms of anxiety, hyperreflexia of the arms and legs, and tremors with vivid color perceptions and optical illusions of brightly illuminated colored patterns. Psychic alterations involve the sense of time, reality, and initiative with euphoria. Insight is retained. Physiological effects may be very marked with nausea, vertigo, mydriasis, and changes in autonomic functions. Individuals differ in the degree and character of their response to mescaline and the dosage may be a critical factor. Hoch and his associates[15] have reported that the mental symptoms produced by mescaline in normal persons are indistinguishable from those produced by LSD. In schizophrenic patients the psychosis may be intensified with uneasiness, apprehension, tension, and panic of varying degrees. Wikler[4] has reviewed these studies.

Most of the reports on mescaline effects in animals deal with autonomic dysfunction. As a substituted phenylethylamine, its autonomic effects might be expected. Intravenously, in cats, mescaline produces defecation, urination, and piloerection. The cardiac and respiratory rates become irregular. Mescaline causes a slight decrease in the amplitude and an increase in the duration of cortical and geniculate electrical potentials evoked by light flashes.[12] It inhibits cerebral synaptic transmission in cats, as do LSD and serotonin.[16] The intraventricular injection of mescaline in conscious cats causes intermittent spikes and slow waves in the electroencephalographic pattern together with crying, howling, and paroxysms of scratching.[16]

Mescaline elicits a variety of stimulant effects followed by depression when administered to different species of animals. The metabolism of mescaline is known to vary in different animal species. For example, the liver of the rabbit has a mescaline oxidase, which inactivates and detoxifies mescaline. This may account for the fact that the rabbit tolerates dosages of mescaline many times greater than those that are toxic to man.

In vitro, mescaline will produce a slight stimulation in cytochrome oxidase activity; succinic dehydrogenase is inhibited. This latter action may be related to the reported antidotal effect of sodium succinate on mescaline psychosis.[14] The acetylcholine content of brains of animals treated with mescaline is not changed.

About $\frac{1}{3}$ of mescaline administered to dogs is excreted unchanged in the urine within four to five hours. In mice 80 per cent is recovered unchanged in the urine. Some of the drug is excreted as trimethoxyphenyl acetic acid. The greatest accumulation of radioactive mescaline injected intraperitoneally in the rat is found in the liver and kidneys, the smallest amount in brain and spinal cord. It is suspected that the high concentration of amine oxidase in liver and kidneys accounts for the localization of mescaline in these organs, although the alkaloid is apparently a poor substrate for the enzyme. We do not know whether or not specific enzymatic effects of LSD and mescaline account for their hallucinogenic actions.

Peretz et al[17] studied trimethoxyphenyl-β-aminopropane (trimethoxyamphetamine, TMA), closely related to mescaline, in man (fig. 3). This substance, given orally,

produced a kind of euphoria and "loosening of emotional restraint" in low dosages. Higher dosages, up to 2 mg./Kg., produced visual hallucinations. Accentuation of the visual imagery was elicited by intermittent photic stimulation. The effects of TMA appeared only after 1 to 1½ hours, about twice as long as required for mescaline.

Clark, Benington and Morin (cited by Fischer[14]) have studied a number of mescaline analogues. Certain tri- di-, and monomethyl substituted β-phenylethylamines induced marked behavioral changes in cats resembling the rage reaction produced by LSD. There was a direct correlation between behavior-modifying compounds and in vitro inhibition of rat brain enzyme systems involving carbohydrate utilization.

Fischer[14] has made the interesting speculation that since hydroxy methylation of epinephrine is involved in its degredation, mescaline, with its three methoxy groups, may inhibit the methylation of norepinephrine in the brain, thus raising its concentration. It is possible that high norephinephrine brain levels may account for the psychotomimetic effects of mescaline. It is unfortunate that we do not have more complete animal pharmacological, behavioral, and biochemical data on mescaline and its derivatives.

Oxidation Products of Adrenaline. The suggestion that adrenaline metabolites were concerned with schizophrenia was made by Hoffer and his associates.[18] These workers proposed that oxidation products of adrenaline, specifically adrenochrome and adrenolutin, may give rise to the hallucinations of schizophrenia (fig. 4). These substances did indeed cause psychological changes in human volunteers, which were like, but not as intense as, a mescaline reaction. However, the changes were not the same as those found in chronic schizophrenia. Intraventricular injections in cats produced an initial drowsiness followed by docility, insensitivity to pain stimuli, and enhanced sexual activity. The electroencephalographic changes were not remarkable. The behavioral effects were not the same as the crying, howling, paroxysms of face, ear-scratching, head-shaking, and rapid, sharp electroencephalographic waves produced by mescaline injections. Marrazzi[19] found adrenolutin and adrenochrome and other psychotomimetics to be synaptic inhibitors in the mammalian brain.

Unfortunately, these oxidized adrenaline derivatives are very unstable in solution and difficult to work with and assay. The fate of these compounds in the body is unknown. Their extreme chemical reactivity may account for their many biochemical and enzymatic actions. Adrenochrome interferes with oxygen consumption by brain tissue in vitro, it uncouples oxidative phosphorylation and inhibits decarboxylation of glutamic acid, it has an antimitotic effect for cells in vivo and in vitro, and it blocks acetylcholine esterase.

The relationship of adrenochrome, adrenolutin, and other adrenaline oxidation products to schizophrenia is of interest. However, until more information has been accumulated, one hesitates to classify these substances as true hallucinogens.

Nalorphine. N-Allylnormorphine is an antagonist to the respiratory depressant action of morphine and certain other narcotic central nervous system depressants (fig. 4). Nalorphine appears to be a competitive antagonist for the brain receptor sites of the target cells of the respiratory centers, and they regain their normal sensitivity to carbon dioxide. The drug may produce visual hallucinations and, in large

intravenous dosages (10 to 30 mg.), extreme anxiety, distortion of body image, and hallucinations of movement, without loss of contact or disorientation. The larger dosages produce a type of toxic psychosis.[4] The agent is a weak hallucinogen.

Piperidyl Benzilate Esters. A new group of psychotomimetic agents was discovered by Abood, Ostfeld, and Biel.[20] These were anticholinergic drugs synthesized as antispasmodics for the treatment of duodenal ulcer. During their therapeutic trials it was found that certain tertiary amine hydrochlorides of benzilate esters, while active anticholinergics, produced hallucinations. The quaternary ammonium salts were entirely devoid of such effects.

In 45 human volunteers, active compounds produced, in 5 to 15 mg. oral doses, megalomanic and paranoid delusions, visual and auditory hallucinations, and a partial loss of contact with the environment. There was no direct relationship between anticholinergic effect and psychotogenic potency. Chemically these agents are esters of piperidine and benzilic acid. The presence of a hydroxyl group in the acid moiety to yield the diphenylacetate ester appears to be essential for hallucinogenic effect. One compound, JB-318, was selected for more extensive trials (fig. 4). This substance is N-ethyl-3-piperidyl benzilate. In a subsequent report[21] the findings with JB-318 were described more fully.

In 39 subjects, volunteers and a heterogeneous group of hospitalized convalescing patients, JB-318 in doses ranging from 5 to 15 mg. orally produced anxiety, somnolence, illusions, visual and auditory hallucinations, decreased immediate recall, and feelings of "unreality" or a "dreamlike" state predictably. In some subjects tactile and olfactory hallucinations, delusions, and ideas of reference were noted. Doses of 20 mg. or greater apparently produced a toxic delirium. There were individual differences in the degree and type of hallucinations and illusions produced by JB-318.

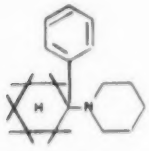
During the course of these experiments it was observed that normal volunteer subjects developed "a change in their basic mood and drive." This change usually appeared one to two days after the experimental session. The subjects became slightly hypomanic and showed increased drive. These observations suggested that agents of this type might be useful in the treatment of mood-depressed psychiatric states. It was found that one compound, JB-329, exhibited psychotogenic properties with a prolonged action. JB-329 is N-ethyl-3-piperidyl cyclopentylphenyl glycolate and is called Ditran (fig. 5). The substitution of a cyclopentyl group for one of the phenyl groups on the benzilic acid side chain gave a compound that produced more hyperactivity and central nervous system stimulation than did its phenyl congener JB-318.

In a preliminary study of the treatment of depressive states, Ditran induced a favorable response in 3 of 5 patients. The initial effect was a bizarre episode that lasted about four hours during which the patient experienced hallucinations, became disoriented and restless, and lost contact with the environment. The desirable postpsychotic effects, which occurred 18 to 36 hours after drug administration, lasted for several days to weeks. Because animal studies showed that the drug was eliminated from the body in 24 to 48 hours, these workers[22] concluded that the therapeutic effects are related to a secondary response triggered by drug administration. It

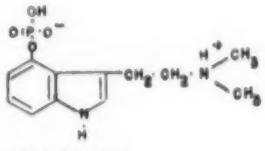
will be of interest to observe if these findings can be extended, for the usefulness of LSD-invoked psychotic-like states appears limited, although admittedly the two classes of drugs produce different effects.

Sernyl and Psilocybin. Only preliminary reports are available on the psychotomimetic properties of Sernyl and psilocybin (fig. 5). Sernyl (1-[1-phenylcyclohexyl] piperidine) was studied pharmacologically and investigated as a general anesthetic. In man the agent elicited a novel psychotic-like state in some patients. The effects differed from those produced by LSD. There was much greater disorganization of thinking and stronger feelings of depersonalization, more fear, more feelings of hopelessness and lack of insight into the self-limited nature of the effect. The drug produced an exacerbation of symptomatology of schizophrenics. Bodi and associates[76] found the drug of limited value in psychoneurotic patients; side effects were prominent, and while decreasing the dose eliminated these reactions, the effectiveness was also decreased.

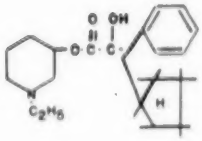
Psilocybin (o-phosphoryl-4-hydroxy-N-dimethyltryptamine) is related chemically to bufotenin and serotonin. The substance was isolated by Hofmann and his associates from species of mushrooms characterized as *Psilocybe mexicana* Heim, which has been used by Mexican Indians since pre-Columbian days in religious rites.[75] The phosphoryl esterified group is novel in a natural product.[77] Psilocybin in doses of 4 to 8 mg. in normal volunteers produced a psychotic-like state grossly resembling that observed after LSD, although the effects did not last as long. The agent produced a state characterized by a strong sense of depersonalization with a deterioration of time sense. Subjects experienced an intense delight from red and yellow colors. Unlike LSD, which tends to excite subjects, psilocybin produced a more tranquil state. The discovery of this hallucinogenic substance and its close chemical rela-



SERNYL



PSILOCYBIN



DITRAN

FIG. 5. Structural formulas of Sernyl, psilocybin, and Ditran.

tionship to numerous compounds of psychopharmacological interest may help to explain biochemical mechanisms within the central nervous system.

THE CHEMICAL NATURE OF PSYCHOTOMIMETIC COMPOUNDS

There seems to be no specific chemical configuration related to psychotomimetic effect, and it is difficult to find a common denominator in such chemically unrelated substances. Specific structural relations in a molecule must be met for psychotomimetic properties. Numerous examples could be cited where slight changes in the structure of an active compound have produced an inactive substance. Ample evidence indicates that the indole nucleus is not necessary for hallucinogenic action.

MECHANISM OF ACTION OF PSYCHOTOMIMETIC CHEMICALS

The information we have at the present time does not permit one to point to an anatomical locus of action, an enzyme system or a biochemical process, specifically involved in the action of these agents. Perhaps one of the most provocative leads has been provided by Marrazzi.[19] The high vulnerability of synapses within the central nervous system to chemicals makes their approach possible. Utilizing the synapses of the optic cortex of the cat activated by transcallosal impulses initiated in one cortex and evoking postsynaptic impulses recorded at the symmetrical point in the opposite cortex, it is possible to evaluate drug responses.

Among the synaptic inhibitors found naturally in the mammalian brain are adrenaline, noradrenaline, and serotonin. According to Marrazzi, substances with a chemical similarity to these agents become candidates for the role of psychotomimetic drugs. Mescaline, adrenochrome, LSD, and bufotenin fulfill these requirements. Indeed, these substances have been found to be synaptic inhibitors and, as pointed out by Marrazzi, their ranking as to psychotomimetic potency in man parallels their ranking as synaptic inhibitors.

Evarts and his associates[22] have studied the postsynaptic lateral geniculate response to single, near-maximal optic nerve stimuli, in cats anesthetized and in cats with implanted electrodes in an unanesthetized state. The intracarotid injection of LSD and bufotenin caused a marked decrease in the amplitude of the postsynaptic response. These workers commented that the sensitivity of the lateral geniculate postsynaptic response to these agents is of the same order of magnitude as the transcallosal response to LSD in the experiments of Marrazzi. It is significant that postsynaptic cortical responses are highly resistant to depression by LSD and bufotenin when geniculate radiation fibers are stimulated. In addition, responses of the optic tract to retinal photic stimulation are resistant to the action of these two drugs. These workers concluded that the geniculate relay represents a point within the central nervous system most sensitive to depression by LSD and bufotenin. Their similar influence on evoked electrical activity in the visual system suggests that the two substances may have fundamentally similar mental effects in man.

Since normal brain function is continuously and critically dependent on the available supply of oxygen and glucose, it would be expected that biochemical disorders would be associated with changes in brain circulation. For the same reason, alter-

ations in the biochemical reactions involving glucose or oxygen utilization would likely be reflected in abnormal brain function. Since LSD and bufotenin are vasoconstrictor agents in isolated preparations, it is reasonable to think that these chemicals might produce changes in brain blood circulation.

Sokoloff et al[29] and others have investigated cerebral blood flow changes in vivo under various conditions. Intravenously injected LSD, in dosages that elicited the characteristic psychological effects, did not produce changes in cerebral blood flow, vascular resistance, or oxygen or glucose utilization in either normal or schizophrenic subjects. A similar lack of change in cerebral blood flow has been found in schizophrenia, during mental activity tests, and after ingestion of chlorpromazine. It is possible that drugs influencing behavior and abnormal mental conditions may be associated with changes in cerebral circulation and metabolism, but the area involved may represent a very small fraction of the total brain vascular supply. Since only the over-all blood flow or metabolism is measured by this method, the effects could not be observed if they took place in a localized minute area. The next obvious step in this approach to the problem of drug action on the brain is the study of the circulation and metabolism of discreet portions of the central nervous system.

PROJECTED DEVELOPMENTS

The possession of these psychotomimetic pharmacological tools, although crude and dull, may permit us to carve our way to a better understanding of the functioning of the central nervous system, in health and in mental disease. Our knowledge of the action of these psychotomimetic chemicals does not permit us to generalize at present on their use in therapy. Perhaps ultimately they may serve their greatest role in stimulating the synthesis of selective, potent compounds that are really precision instruments—scalpels for chemical dissection of brain function.

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PIPERAZINE FOR UROLITHOLYSIS. Intraureteral piperazine for urolitholysis permitted successful nonoperative treatment of calculous anuria in 2 patients, both with single kidneys (Sem. hôp. Paris 35:1604, 1959). In 1 case the patient had barely withstood earlier ureterostomy and then nephrostomy. Ureteral instillation of concentrated (4 Gm./100 cc.) aqueous solution of piperazine dissolved the calculi completely within three to five days.

"DENERVATION" FOR ARTHRITIS. A "denervation" operation to provide relief from arthritic pain was recently reported by R. A. Herfort (White Plains, N. Y.). The procedure, which involves surgical removal of trunk ganglia and plexuses, was performed on 8 patients with rheumatoid arthritis and 18 with osteoarthritis. Continued improvement in all cases was shown in a follow-up study of 4½ years.

NUTRITIONAL FORMULA. Indicated for medical and surgical patients to help speed recovery is a capsule containing ascorbic acid, citrus bioflavonoid compound, thiamine mononitrate, riboflavin, pyridoxine, vitamin B_{12}, niacinamide, panthenol, choline, inositol, desiccated liver, and yeast. It is marketed as C-B Vone capsules by U. S. Vitamin and Pharmaceutical Corp.

OPERATION FOR DISC DEGENERATION. An "interbody fusion" operation to correct disc degeneration in the neck is being used by Ralph B. Cloward (Honolulu, Hawaii). An incision is made in the front of the neck so the disc can be reached directly without the spinal cord being in the way. The flattened disc is removed, and a bone (usually taken from a bone bank) is inserted.

NEW ANORECTIC DRUG. A new anorectic drug (Ionamin, R. J. Strasenburgh) was tested in 178 obese patients in dosages of 15 to 60 mg. given in the morning (Am. J. M. Sc. 238: 55, 1959). The drug was found to be effective in reducing appetite in 70 to 80 per cent of patients. There was an average weight loss of 0.25 lb./patient/day. Side effects were insomnia, constipation, or nervousness, seen in about 12 per cent of patients.

COMBINED VACCINE APPROVED. A combined four-in-one vaccine that immunizes against poliomyelitis, diphtheria, pertussis, and tetanus has been approved by the U. S. Public Health Service and is now available. Parke, Davis

& Co. and Merck Sharp & Dohme are the first pharmaceutical firms licensed to manufacture the new vaccine, which is intended only for children less than 5 years old. Inoculations are given in three doses, a month apart, with a fourth injection of poliomyelitis vaccine administered five months later for optimal protection. The new vaccine is considered unsatisfactory for immunizing older children and adults because of the greater incidence of sensitivity to diphtheria toxoid in these age groups.

UNILATERAL NEPHROANGIOGRAPHY. Unilateral nephroangiography (introducing the catheter through the brachial artery) greatly aided preoperative diagnosis in 3 patients with renal neoplasms (Minerva urol. 11:65, 1959). Usual laboratory and radiographic studies, including retropneumoperitoneum and pyelography, had given inadequate data on extent of the lesion and its nature. Selective renal angiograms immediately revealed not only the vascular pattern pathognomonic of tumor, but also the optimal surgical approach.

ANTIEMETIC. A new phenothiazine compound is pipamazine (Mornidine, Searle), which acts on the medullary emetic center to prevent or stop nausea or vomiting associated with anesthesia, pregnancy, and radiotherapy. The drug is reported to have minimal ataractic and sedating activity, although drowsiness may be experienced by some patients. The same precautions should be observed as with other phenothiazines.

EXPERIMENTAL STUDIES OF ASTHMA. Severe asthmatic attacks ending in death may be prevented experimentally in dogs by severing the vagus nerve, reported Gardner Middlebrook (National Jewish Hospital, Denver). It was found that by cutting the vagus nerve of dogs with status asthmaticus, the fatal attacks were prevented. In the condition, a heart disturbance results from nerve impulses transmitted by the vagus from the lungs to the heart.

ANTIDEPRESSANT. A potent new monamine oxidase inhibitor is B-phenylisopropylhydrazine, supplied as the hydrochloride (Catron, Lakeside), reported to be capable of inhibiting monamine oxidase in the brain without interfering with this enzyme in the liver. The action of the drug is rapid with prolonged therapeutic effect when given in low dosages. It is indicated for treating mental depressions and those associated with certain chronic diseases, such as angina pectoris and rheumatoid arthritis; in very small dosages the drug is useful as an adjunct to psychotherapy.

The Epic of Medicine (IV)

A TORRENT OF LIONS*

(Medicine in Imperial Rome)

(285 B.C.-A.D. 476)

Félix Martí-Ibáñez, M.D.

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Like a torrent of lions the Romans fell upon the historical scene, and their proud imperial eagles swept across the skies of the world.

Strong warriors the Romans were, as well as highly adept in law and administration. Originally a handful of Aryan merchants ruled by Etruscan kings, the Romans created an aristocratic republic, with a caste of patrician families lording it over the masses. Their history encompasses bloody triumvirates, mighty emperors—sadists and philosophers, schizophrenics and saints—who created a vast and powerful empire, only to succumb to a plague and inflation. Military curse of the world, Rome was redeemed by its genius in jurisprudence and organization, by its men of letters, its patricians, and, above all, its physicians.

Mining and agriculture for slaves and laborers, and war for all and at all moments, were the main occupations, which engendered an aristocracy of force. A world of athletes and adventurers, empire of the javelin and the lance, the sword and the bow, the Romans ascribed great importance to that *offensive* weapon par excellence—the shield, for no one who is innocent of the desire to attack his fellow men would trouble to provide himself in advance with a means for protection.

The Romans boasted of splendid brick, clay, and marble cities, with fine torch-lit streets and wide roads. They made exquisite painted ceramics and porcelains, wrote on parchment (nontanned lamb hide), had arsenals and central heating, travel agencies, draining canals, food inspectors, and military hospitals. In their *prandium* and *convivium* they ate bean porridge and nonfermented bread dipped in honey, and drank diluted wine and oxymel. Their technology was based on slavery until they realized that horses, though they ate more than slaves, were stronger and therefore more economical. Their art reflected their megalomania for the colossal, just as Greek art reflected a craving for beauty. With its triumphal arches and colonnades, vast coliseums and arenas, Roman art epitomized the Roman cult of force.

Originally Roman medicine was magical. When the pendulum of world knowledge swung to Rome, side by side with the Aesculapian cult there flourished all sorts of quacks who dealt in wholesale healing, though often their only medication was goat fat or, as in the case of Cato the Censor, cabbage juice, which he prescribed

* This is an expanded version of the editorial that appeared in *MD* Medical Newsmagazine, November, 1959. It is the fourth of a series of twelve devoted to presenting a philosophical outline of the history of Medicine.

for all ailments alike. He even ordered his patients to bathe in the urine of persons who had fed on cabbage and with his experiments finally succeeded in killing his own wife.

For a long time practiced only by priests, which therefore made it inferior to philosophy and poetry, medicine was left chiefly in the hands of slaves, until the first Greek physicians arrived in Rome, particularly Asclepiades of Bithynia, who with his golden tongue conquered Rome and created a solidistic philosophical system based on the notion of atoms. Thereafter several schools of thought flourished. There were Methodists—Themison of Laodicea and the great gynecologist Soranus of Ephesus—who considered disease an alteration in the organic pores and thus simplified the treatment of the great masses of slaves in the plantations; Pneumatists—Athenaeus of Attalia, Archigenes and Aretaeus of Cappadoccia—who recognized as vital force the *pneuma*, or soul of the world, any alterations wherein produced disease; and Eclectics, such as Pliny the Elder, Dioscorides, the naturalist and master of medicinal plants, Rufus of Ephesus, almost as great as Galen, and the elegant, sophisticated, erudite Celsus, of golden Ciceronian eloquence.

The first physicians in Rome were slaves. Later they became *medici liberti manumittidis*, when Julius Cesar granted freedom to all freeborn Greek physicians practicing in Roman territory. A kind emperor, Antoninus Pius, instituted state regulations protecting municipal physicians, enabling some of them, Antonius Musa, for instance, to amass great fortunes and, though they were only liberated slaves, to be honored with monuments. Physician-slaves, on the other hand, could be bought for some $340, less $60 if they had been castrated. Physicians of the invincible Roman legions and of military hospitals or *valetudinaria* coexisted with palatine or imperial physicians and with "specialists." After the establishment of medical licenses in A.D. 200, medical societies and civil hospitals were created, and imperial laws for medical students, such as the one prohibiting the visit to brothels, were passed, much to the grief of the students.

Even then therapeutics comprised magic. Next to the polished effigies of the new gods hung ancient Etruscan mirrors of polished bronze engraved with images of succubi. A barbaric polypharmacy (turtle blood, camel's brains, crocodile excrement) was used as much as new drugs and techniques in the treatment of epilepsy. Fear of touching the dead body paralyzed all progress in anatomy, which was studied only in animals and during vivisection of criminals. To study the great organic cavities, so feared by the ancients, they dared practice short and quick—to forestall putrefaction—dissections in Barbary monkeys.

The most important Roman contributions to public health were the marvelous aqueducts, which to this day make Rome the best irrigated city in Italy, public baths and swimming pools, sewers, fountains, and wells. At its zenith, Rome could boast of having more than 122 gallons of water per inhabitant. Yet, the poor had to bathe in the Tiber, the streets were filth ridden, and in small towns and villages excrement streamed down the streets. The Romans had public health inspectors, but personal hygiene degenerated into an end instead of a means, into effeminacy and depravation. Sports evolved into athletics, and hygiene into weakness. Later, with Christianity, the body was neglected and the filthy body became the only pos-

sible dwelling for the pure soul, and the naked Greek statuary of fluid line was replaced by the rigid, austerely robed statuary of Christianity. Overindulgence in the pleasures of the body—banquets of succulent, highly spiced food, torrents of wine and hydromel (the Roman Coca-Cola), torpid siestas in the shady atrium, massages at the sensuous hands of expert slave girls—set the Romans far on the road to degeneration and destruction. Little or nothing could the Roman physician do against all this, even if the physician was the great Claudius Galen.

To this day Galen excites a feeling of ambivalence among physicians. Since Roman medicine is linked to such unpleasant things as slavery and dogmatism, which is exactly the opposite to what medical progress requires, that is, a climate of absolute freedom, Galen's glory must be constantly revindicated. But Galen, whose word and work were articles of faith for fifteen hundred years, is really a *modern* author.

Born at Pergamum, Galen was baptized Galenos, meaning a tranquil sea, he who was so atrabilious! In his seventy years of life, he served as physician first to gladiators and later to the Roman emperors—Marcus Aurelius, the gentle philosopher, Commodus, Pertinax, Didius Julianus, and Septimius Severus. Galen conquered the Imperial City with his gifted tongue and his great culture, and he left a pyramid of more than 500 works, which would be the basis of his dictatorship in Medicine for fifteen centuries. His anatomy, based exclusively on dissection of monkeys and only two human corpses, was nevertheless correct, his physiology and pathology were speculative, his therapy was empirical; and his endorsement of the Aristotelian notion that the body is the vehicle of the soul was the basis for the monotheism of Arabs and Christians.

Galen believed in the Hippocratic nosology and in humoral pathology to the effect that the blood *moved*, not circulated, through the arteries; he also accepted that the body was made of *parts*, not humors. Later, in the Renaissance, Paracelsus would destroy Galen's pathology; Vesalius, his anatomy; and Paré, his "first intention cures." Galen's theological viewpoint, which made him the spoiled child of Christian psalmists, did great damage to his physiological investigations.

While Hippocratic medicine was humoral and philosophical and therefore antiquated, Galenic medicine was anatomic and consequently modern. His concept of a *pneuma* breathed by man, which at his death returned to its source of origin, becoming a universal *pneuma*, accepted that such a spirit turned into *natural* spirits in the liver, was distributed through the veins and transformed into *vital* spirits upon reaching the left heart, was then distributed through the arteries and finally became *animal* spirits in the brain, and was then distributed through its "branches," the nerves.

Galen initiated the use of "Galenicals" or vegetable simples and turned practical hygiene into applied physiology—the Eclectic application of rest, diet, sleep, and exercise. In accepting the Aristotelian concept of the relation between body and soul, the responsibility of the individual, and the Christian interpretation of life, Galen once again reunited medicine and philosophy, which had been separated by Hippocrates.

After Galen, Christianity imposed a curative religion and disease became an act

of purification and divine grace. Galen's disciples were excommunicated and priest-healers were glorified. Upon his death, Galen's writings disappeared and were not resuscitated until they were translated into Latin in the thirteenth century, which helped prolong the cultural coma that was to last one thousand years. In decreeing that every human organ was made perfect by the Creator, Christianity discouraged anatomical studies and experimental medical research.

The Roman contribution to the progress of mankind included improved collective hygiene and public health, irrigation, draining, aqueducts, thermal baths, gymnasia, inspection of markets and brothels, antimalarial measures, military hospitals, legalization of the medical class by such means as title-licenses and examinations, medical insurance, social and military medicine, systematization of medical instruction, and a higher social standing for the physician.

Until one day the boots of barbarians from the North invaded Rome and trampled the imperial purple and the blood-soaked togas strewn all over the floor of the Roman Capitol, which rang with the clang of bronze and steel, announcing the beginning of the Middle Ages.

SYMPOSIUM ON MEDICINE AND WRITING

The Symposium on Medicine and Writing that appeared in the November 1956 issue of INTERNATIONAL RECORD OF MEDICINE has been published recently as a Monograph. The articles included in this Monograph are: "The Editing of a Modern Medical Textbook" by Russell L. Cecil; "Plain Talk and Clear Writing" by Morris Fishbein; "The Principles of Bibliographic Citation" by John F. Fulton; "The Art of Communication" by Joseph Garland; "On Writing a History of Medicine" by Douglas Guthrie; and "Minerva and Aesculapius: The Physician as Writer" by Félix Martí-Ibáñez.

This 72-page Monograph is sold for $3.00. As the fourth in the series of MD International Symposia, this book is the companion piece of *Medical Writing*, which was published in May 1956.

To obtain this monograph, write to MD Publications, Inc., 30 East 60th Street, New York 22, N. Y.

BOOK REVIEWS

The Amphetamines: Their Actions and Uses. CHAUNCEY D. LEAKE, PH.D. Springfield, Ill., Charles C Thomas, 1958. Pp. 167.

In this outstanding book, humanist and distinguished medical historian Dr. Chauncey D. Leake, Professor of Pharmacology at The Ohio State University, has provided a concise, excellent survey of our scientific knowledge of the amphetamines. Since the author addresses himself to a wide audience of physicians, lawyers, administrators, sociologists, law-givers, and others, he has wisely omitted details of chemistry and physicochemical aspects of the amphetamines. Instead he surveys the most important aspects of the history, pharmacology, pharmacodynamics, and therapeutic uses of the amphetamines from an over-all viewpoint, using that wide perspective of the true man of science.

One of the most interesting chapters is Dr. Leake's discussion of sociological aspects of the use and abuse of the amphetamines. These drugs have been occasionally denounced as causing "addiction" or other harmful effects and as being used without proper medical indication to achieve various effects. Dr. Leake concludes:

> . . . it seems that the long experience in the medical use of these drugs has shown their real worth in the management of many important medical conditions, and has indicated the factors that may result in their occasional abuse. From the standpoint of addiction or habituation, or with regard to unsportsmanlike abuse in physical contests, or in reference to abuse by immature persons wanting to get pepped-up for a thrill, or from the position of restrictive legislation, the amphetamines are relatively safe, as they are in proper medical use. The exercise of good-sense, with appropriate education, on the part of lawmakers and administrators, will probably keep their abuse to a minimum. The amphetamines are valuable drugs. They are widely and safely used in many serious diseases, and for the improvement and betterment of human behavior.

The book also contains valuable discussions of physical properties of the amphetamines, their absorption, fate, and excretion, general pharmacology, toxicity, therapeutic use. A comprehensive bibliography completes this significant study, which is a model of what a book on new drugs should be: concise, objective, unbiased, and tersely written for the purpose of enlightenment and guidance of the reader.

Mirage of Health. RENE DUBOS. New York, Harper & Brothers, 1959.

Current concepts of health are interpreted philosophically in this monograph on world perspectives. The author maintains that complete freedom from disease is almost incompatible with the process of living; hence mankind's dream of perfect health is not only impossible but impractical. Indeed, an aseptic world would be dangerous and dull.

Dr. Dubos unravels a medical panorama of incredible scope embracing society from its inception and all the ramifications evolved by its inhabitants, and demonstrates the commanding influence that disease has had on cultures, politics, and warfare.

The chapters range from the Garden of Eden to the biological adaptation of human

struggle and environmental effects on disease processes, social patterns in disease, changing civilizations in health and disease, and human goals.

The work integrates all aspects of culture as they impinge on health as an ever-sought human objective.—*I. Neuton Kugelmass, M.D.*

Principles of Biochemistry. ABRAHAM WHITE, PH.D., PHILIP HANDLER, PH.D., EMIL L. SMITH, AND DE WITT STETTEN, JR., M.D., PH.D. New York, McGraw-Hill Book Co., 1959.

The extraordinarily rapid expansion of knowledge in biochemistry has led to this very valuable second edition. It unravels the chemical factors regulating normal function as well as their alterations in disease processes. The format of the book remains the same, stressing the basic principle of mammalian biochemistry and illustrating the principles by reference to human species. Considerable emphasis is given to comparative biochemistry since processes in lower forms often provide an insight into biochemical mechanisms in higher forms. There are extensive descriptions of chemical reactions not duplicated by mammals, e.g., photosynthesis and the synthesis of essential amino acids.

The book is divided into seven parts: the composition of living matter, the functional dynamics involving catalysis, metabolic phenomena involving chemical components and their catalyzed reactions, composition of body fluids and the effects of variations, the biochemistry of specialized tissues and organs interpreting unusual types of bodily function, biochemistry of endocrine glands unraveling the physiological regulators of mammalian homeostasis, and, finally, the role of nutrition in cellular dynamics.—*I. Neuton Kugelmass, M.D.*

Tranquilizing Drugs. Arranged and edited by HAROLD E. HIMWICH. Washington, D. C., American Association for the Advancement of Science, publication no. 46, 1957.

Ataractic drugs are clarified on the basis of over-all action on human beings as hallucinogens, ataraxics, and central stimulants. Chemical classification is presented for data on the structure-action relations. The contributions include electrophysiological analysis of ataractic drug action, metabolic analysis of drug action, and therapeutic procedures with ataractic drugs. Hallucinogens are indoles that dissociate neuronal association pathways. They break the nervous integration in healthy persons, inducing a transitory schizophrenic effect with consequent depression. The ataraxics are mildly depressant and induce muscular relaxation. The cerebral stimulants increase alertness, blood pressure, and muscle tone, and exaggerate the reflexes. The absence of an anatomical structure corresponding to the blood-brain barrier does not deter the concept of a chemical gradient between the body circulation and the brain cells and brain stem via enzyme systems. It is a protective mechanism to prevent chemical action on the brain. The functional role of the brain barrier in the mechanism of ataractic action is discussed experimentally and chemically in this series of contributions by American and Canadian workers.—*I. Neuton Kugelmass, M.D.*

A New MD Medical History...

A HISTORY *of* OPHTHALMOLOGY

by George E. Arrington, Jr., M.D.

Associate in Ophthalmology, Medical College of Virginia, Richmond, Virginia

A HISTORY OF OPHTHALMOLOGY provides an over-all view of ophthalmological progress through the ages. With scholarship and originality the author traces the thinking, of men known and unknown, that has made possible the technological advances of this science. Man's search for understanding of vision and its preservation is shown effectively in its relation to the history of civilization. The content of this book ranges from the period of prehistorical ophthalmology to the present day. In emphasizing the effect of related sciences, philosophy, and human culture upon ophthalmology, Dr. Arrington offers new insight into his subject. Appropriate attention is given the ascendancy of modern ophthalmology including an evaluation of its current trends in the light of the future. It is a book of interest to ophthalmologists, general practitioners, and students.

This volume is one of a series devoted to the histories of various specialties and facets of medicine. Félix Martí-Ibáñez, M.D., who wrote the foreword to A HISTORY OF OPHTHALMOLOGY, is the Editorial Director of the series, which includes books on Public Health and Neurology.

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